

Global Status of Advanced / Metastatic Breast Cancer

2005 - 2015 Decade Report



FINAL REPORT – March 2016

This report is dedicated to the patients around the world who are facing, will face, or who have already lost their lives to metastatic breast cancer far too soon. It is our promise to you and your loved ones that *you are not alone in this battle.*

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Foreword

Since 2000, when I finished my specialization, I have devoted my career as a medical oncologist to caring for women with breast cancer, and I have developed a particular interest in treating those with advanced, or metastatic, disease (also called secondary breast cancer in some countries). Unfortunately, we – the breast cancer medical community – have not made the progress that my colleagues and I would like to see in treating this disease. Like most advanced cancers, metastatic breast cancer (mBC) is incurable, and it is responsible for half a million of untimely deaths of women – and some men – around the world each year.

There are major shortcomings in the treatment and management of mBC. Median survival has remained for many decades at 2 to 3 years after diagnosis. Our research strategies need a comprehensive overhaul if we are to make progress, by better international collaboration on large, well-designed clinical trials with truly meaningful endpoints/objectives, and smarter analysis of the large amount of biological data being gathered.

What is also apparent is that, across the spectrum, from healthcare professionals to society -- every cancer patient no matter where she or he lives has not successfully received the current standards of care and support. In particular, there are shocking disparities between developed and developing countries, with many more in the latter diagnosed at an advanced stage. This exposes a lack of early detection and proper access to services across the care spectrum.

Further, health professionals can add to the concerns of patients when they are not clear about the status of the disease and goals of treatment, or when they do not offer care according to guidelines. It is certainly not easy to talk to patients and families about an incurable disease, but it is essential to do so, and to give clear information about treatments that should be offered. Disparities in access to good quality cancer care have become a sad reality, not just between countries but within each country as well.

Additionally, it is clear that patients globally face stigma and isolation from their communities when they are diagnosed with mBC, a time when they are most in need of high-quality support. Unfortunately, societies, including the advocacy community, have done little to raise awareness of advanced disease and the negative perceptions patients can face from employers, insurers, and indeed, even family and friends.

Progress has been made to move management of this disease forward in the past few years. The ABC (Advanced Breast Cancer) conference established the first international consensus guidelines for advanced and metastatic breast cancer, which provide not only medical standards of care, but also guidance on psychosocial and specialist support. The 3rd ABC conference in 2015 was the launch pad for *The Global Status of Metastatic Breast Cancer: A Decade Report*, which builds substantially on previous initiatives.



There are so many things to learn about the needs of these patients and how to address them. Astonishingly, we do not even precisely know how many women and men are living with advanced breast cancer in each country. How can resources be accurately distributed if we do not know how many patients actually need them?

Previous international surveys, such as the 2006 Silent Voices Survey and the 2009 BRIDGE survey, showed that mBC receives inadequate attention globally, and that information for patients is often lacking. That has led to several global but also national and local efforts, calling for more investment in research, implementation of high-quality international guidelines, equal access to care and support, adequate cancer registries, and dedicated advocacy groups.

But has the landscape of mBC really changed since these earlier surveys? Have the efforts so far truly improved the well-being of these patients?

The breast cancer community urgently needs a more comprehensive picture and solid evidence to answer these questions; this led to *The Global Status of Metastatic Breast Cancer: A Decade Report*. This report is now one of the most far-reaching analyses of the key factors that together will contribute to improving the care and well-being of those diagnosed with mBC. It is informed by multiple surveys on public awareness, patient support, societal experience, and cancer center/hospital services around the world, paired with commentary on scientific progress and the policy landscape. A few key findings are below.

First, the report identifies quality of life among the main patient concerns. Quality of life – the ability to enjoy life as free as possible from the physical, emotional, and financial burdens of the disease – is crucial for patients. More research is needed to assess how factors such as these can affect each person. Findings related to public awareness are also surprising, as we found that many people in various countries would rather not hear patients talk about their metastatic cancer, or that patients are somehow to blame for their illness. These attitudes must be tackled if quality of life for advanced cancer patients is to improve. Analysis of the direct and indirect economic impact identified excess financial impact and associated distress of mBC on patients and their families/caregivers, particularly at the end-of-life, compared to eBC.

The report's original research on breast cancer centers show that many healthcare providers fall short in offering patients much-needed resources and activities, such as metastatic-specific information, and referral to peer support. Also, important discussions with patients and caregivers about complex treatment decisions, supportive care, and end-of-life care often do not happen. This is why pushing for the adoption of guidelines, in particular the ABC international consensus guidelines, is vital. In some centers around the world, mBC patients are not discussed and managed in a multidisciplinary way, failing to provide the best possible care for each person.

Finally, the report details a slowdown in the pace of scientific innovation. The gap is stark, especially when compared with other cancers, such as lung and melanoma, for which significant advances have been made over the past 2 to 3 years. There is an urgent need for new, high-quality metastatic breast cancer research, as mBC is lagging behind other tumor types. We need urgently to discover new therapies, but also better understand which patients benefit from the different treatments, so as to better allocate resources.



I welcome this report and Pfizer's commitment to publishing these data to further our understanding of mBC, and I hope that it energizes and unites those in the cancer community. I am also grateful to the dedication and crucial involvement of all the members of the steering committee who, with their expertise and independence, have helped shape this important piece of research.

United, we will define a "call to action," with achievable objectives for the next decade. This will help those in the cancer community guide policymakers as to what steps can be taken to match best practices in caring for a major and vulnerable group of patients, point them towards better research strategies, and above all ensure that the issues rise up to – and remain at – the top of health and well-being agendas.

Advanced breast cancer patients, the true heroes in this relentless fight, count on all of us!

Sincerely,



Fatima Cardoso, MD

*Chairperson, Global Status of mBC Decade Report Steering Committee
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Please see full
Steering Committee
biographies, starting
on page 167.



This report was shaped through the generous guidance and feedback from the Steering Committee Members. The organization logos are meant to show Steering Committee affiliations and do not imply endorsement of the opinions of the report by their respective organizations.

Report Introduction

The *Global Status of Advanced/Metastatic Breast Cancer 2005-2015 Decade Report* is the first globally focused assessment of advanced/metastatic breast cancer (mBC), across the care continuum, political, economic, societal and scientific landscapes. Pfizer Inc., working collaboratively with the European School of Oncology (ESO) and within the scope of the Advanced Breast Cancer Third International Consensus Conference (ABC3), commissioned this report, which will reveal both areas of improvement and substantial gaps in care, access to resources and support, and treatment outcomes for patients with mBC. The goal is to inspire those who care for patients directly as well as those responsible for shaping the way care is delivered. We hope to see these individuals, together with the general public, work alongside one another in developing solutions that will further meet the complex and unique needs of patients with mBC. It is recognized that mBC management and support has improved over the past decade; however, significant gaps still remain. This progress has not nearly kept pace with the evolution witnessed in managing early breast cancer (eBC).

This report outlines the baseline from which emerging recommendations can be developed, to advance care and outcomes for patients with mBC over the next 10 years.

Prior Research

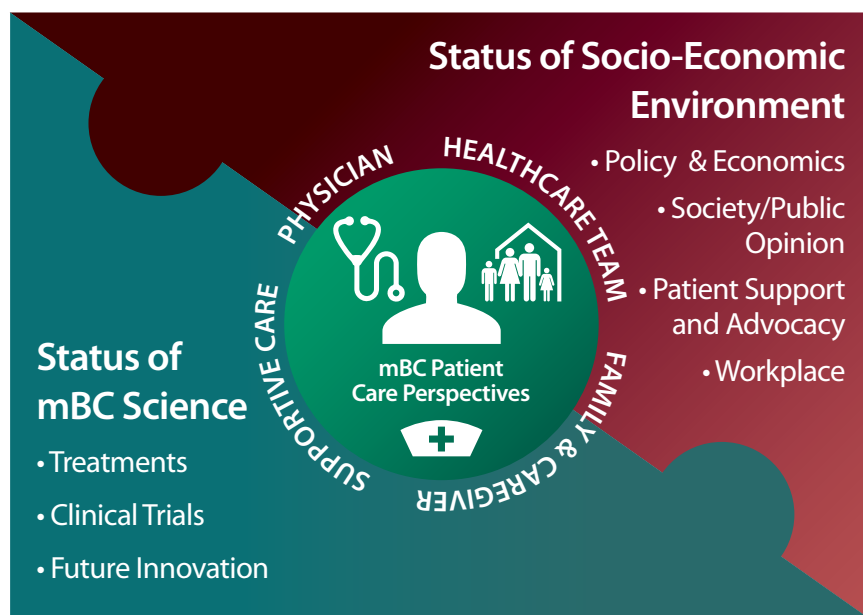
Two mBC reports in particular were influential in exploring the mBC landscape, and serve as the building blocks from which this report stemmed. The first, the landmark 'BRIDGE' survey, conducted in 2008 and 2009, and published in 2010, revealed huge unmet needs across the 1,342 women with mBC across 13 countries. (BRIDGE Metastatic Breast Cancer Patient Survey, 2010) At the time of its publication, key issues identified included both the need for more public attention on understanding mBC, and patients' desire to be included amongst the broader breast cancer community. Shame, silence, and isolation were described as the hallmarks of mBC. The second report, the 2014 MBC Alliance Landscape Analysis in the USA, described the care environment for mBC patients, with a particular focus on quality of life. It discussed topics such as psychosocial distress and emotional support, information needs, communication and decision making, relief of physical symptoms and practical concerns including work and finances, and research funding.

Both reports began to shed light on the significantly different needs and experiences patients with metastatic disease face, especially in comparison to those with early stage disease. What was yet to be understood is how these findings translate to a global level, and which additional factors require consideration and understanding. One of the critical areas not looked at in the previous landscape reports is the extent of scientific progress and innovation in mBC across the last decade, after significant leaps in the 80s and 90s. Systematic and comprehensive global evaluation of the last 10 years is critical to build a strong foundation of knowledge on which communities can take steps towards a multi-stakeholder drive for change.



Figure A

Multilayered Approach to Assessing the Status of mBC



In order to effectively assess the status of mBC globally, there are multiple factors that need to be evaluated. For this assessment of the global status of mBC, the net has been cast wide, with the aim of providing a holistic viewpoint. Figure A demonstrates the multilayered approach taken to understanding the elements that impact patients with mBC.

Research Approach

Research has been conducted under the 3 overarching themes outlined in the multilayered approach to assessing the status of mBC. The report contains 3 core sections, each comprising focused chapters (Figure B).

A comprehensive analysis was conducted comprising both secondary research and primary research to inform these sections.

Secondary research was conducted using in-depth scientific literature reviews of peer-reviewed publications, patient survey reports, and media/online articles in order to understand the current landscape of mBC care. More than 3,000 previously published articles and abstracts from PubMed, Medline, Cochrane Library, and Breast Cancer Conferences were analyzed via several different literature searches in development of the report with the aim of ensuring a robust, evidence-based approach.

Full details of all literature searches are contained in the appendices of this report. Published data was often from sources based in high-income countries, with some gaps remaining in reliable information from low- and middle-income countries. While there is commonality in many of the personal challenges facing patients with mBC, the country in which they live is very influential on whether they are diagnosed, treated, supported appropriately, and ultimately die with dignity or without suffering. Even after the launch of the first version of this report, ongoing environmental monitoring of the media and major medical conferences identified emerging research relevant to this report. As such, additional data has been added to sections 1 and 2.

Primary research was conducted in 2015 and 2016 in the form of 4 global qualitative and quantitative research surveys with the general population, patient support organizations, breast cancer centers, and patients and caregivers to address areas not covered in secondary literature and uncover new insights. This research included nearly 15,000 individuals in 34 countries (see Figures C and D).



Figure B

Global Status of mBC Decade Report Overview

| Patient Care Perspectives | Policy, Society and Community Impact | Scientific Landscape |
|--|---|--|
| <ul style="list-style-type: none"> • Information and Communication Needs • Decision Making • Quality of Life and Daily Living • Supportive Care along the mBC Continuum • End-of-Life Care • Approaches to Delivering mBC Care: Cancer Center Profiles | <ul style="list-style-type: none"> • Health Policy of mBC • Economic Burden of mBC • Public Understanding of mBC • Impact of Patient Support and Advocacy Organizations in mBC • Workplace Perspectives in mBC • Impact of mBC on Caregivers and Social Relationships | <ul style="list-style-type: none"> • Global Burden of Breast Cancer • History of Progress in Breast Cancer • mBC Innovation Plateau • Focus for the Future |

Respondents included the general public, patient support organization leaders, oncologists, oncology nurses, breast cancer center administrators, mBC patients, and caregivers. Detailed reports for each survey are provided as appendices; however, key data points and top-line conclusions are reflected in this report. It is important to recognize that primary research results for this report were defined by local access to the phone and

internet. Responses were gathered either online, by telephone or through face-to-face interviews with respondents.

Supplemental, qualitative in-depth interviews were conducted with leadership of patient support organizations and healthcare providers in sub-Saharan Africa, to provide additional perspective to the relatively few mBC specific secondary data sources for this region overall.

Figure C

Overview of Global Reach Across Quantitative and Qualitative Research

| Survey | mBC General Population Survey | mBC Patient Support Organization Survey | Breast Cancer Center Survey | mBC Patient and Caregiver Qualitative Research* |
|-----------------------|-------------------------------|--|--|---|
| Number of Respondents | 14,315 | 50 | 582 | 28 |
| Number of Countries | 14 | 28 | 9 | 7 |
| Respondent Type | Adults, 18+ years | CEOs, presidents, directors, etc of charitable and non-profit organizations that focus on metastatic breast cancer, breast cancer, and/or cancer | Breast Cancer Center leaders (C-level, administrator, medical director of oncology), oncologists, gynecologists (Germany), oncology nurses | Patients with mBC and caregivers of patients with mBC |

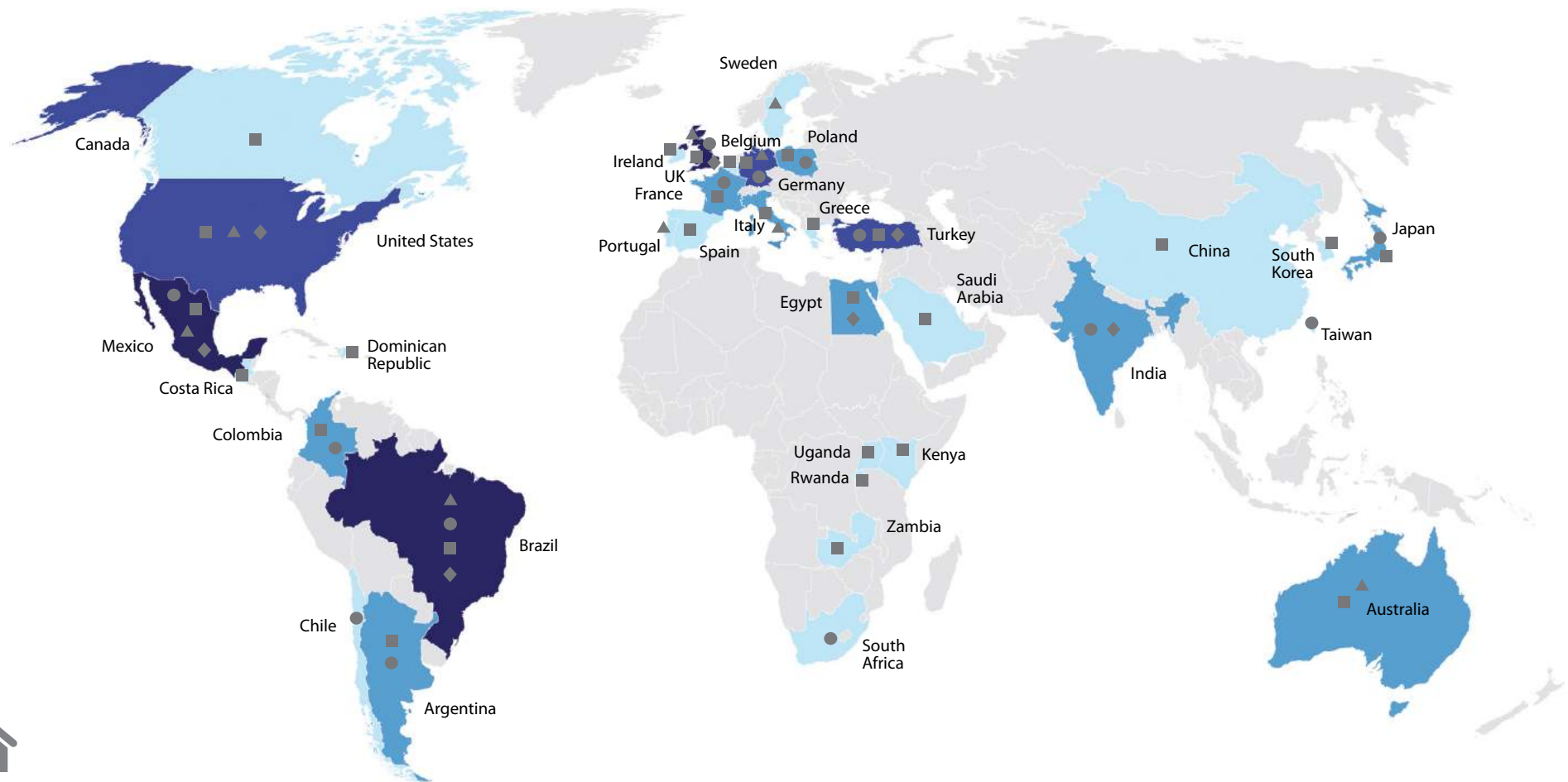
*Please see the Primary Research Appendices page 237



Figure D

2015 and 2016 mBC Primary Quantitative and Qualitative Research

- mBC General Population Survey (n=14,315)
- mBC Patient Support Organization Survey (n=50)
- ▲ Breast Cancer Center Survey (n=582)
- ◆ mBC Patient and Caregiver Qualitative Research (n=28)
- Countries represented one time
- Countries represented two times
- Countries represented three times
- Countries represented four times



In addition, in-depth interviews of 6 breast cancer centers in Argentina, France, India, Lebanon and the United States were conducted. The goal was to identify and highlight unique approaches to the care of patients with mBC, tailored to local patient needs and socio-economic context. Interviewees were oncologists, nurses, and cancer center directors. The intention is not to draw comparisons between centers or countries, instead the aim is to highlight different ways in which patients with mBC receive care and hopefully provide useful insights to the readers of this report for consideration in local practice.

Ongoing Work

Work does not stop with this report. It is hoped that results published in this report will be used to stimulate discussion across the world, inspire education and drive change in the care of patients with mBC.

Naturally, it is difficult to draw conclusions and make recommendations with a 'one-size-fits-all' approach. In authoring this report, there have been areas where an opportunity to advance care in the future was identified and these are captured under "Emerging Recommendations" at the end of each chapter. However, there needs to be broader discussion and dialogue on the findings of the report to further develop the recommendations; ultimately a comprehensive charter with appropriate goals needs to be created outside of this report. Such a charter would incorporate the observations made within this report and provide a blueprint that the breast cancer community can work towards.

Contributors

Development of the report could not have been achieved without the support of the Global Status of mBC 2015 Decade Report Steering Committee who provided guidance and direction throughout the process, the European School of Oncology, and Advanced Breast Cancer Consensus Conference (ABC3). A Steering Committee of global multidisciplinary mBC advisors, composed of physicians, patient support organization leaders, and patients, provided valuable perspectives and integral direction and feedback that have enriched and shaped the report. Meet our steering committee on page 5.

ESO, Pfizer, ABC3, and the Steering Committee would like to acknowledge the significant and powerful work that has been done to date, particularly the healthcare practitioners (clinicians, nurses), patient support/charitable organizations and experts that have taken the time to publish their work, share their experiences and build a stronger foundation, one brick at a time. Information has been included from a multitude of experts in this report – every opinion matters.

Sincere thanks are offered to those who took the time to share their thoughts and experience – each and every perspective helped to bring this report to life.



Terminology and Considerations

In reading the report, there are some nuances in use of terminology to note:

- Approximately 99% of patients with mBC are female (Cancer Experience Registry Report, 2013–2014); little information was identified regarding men and as such, the narrative of this report refers to women most frequently. However, the conclusions while built largely in response to data about women, cannot equally apply to men. In many cases male needs are likely to be similar; however, specific research is needed to understand how men's needs differ from those of women
- Throughout this report mBC is referenced as the particular disease state of interest, however research was conducted to include the terms "advanced breast cancer," "metastatic breast cancer," "secondary breast cancer," and "stage IV breast cancer" to ensure all useful secondary research was collected
- The terms supportive and palliative care are frequently used interchangeably. For the purposes of this report, supportive care is defined as the prevention and management of the effects associated with the disease itself or its treatment, while palliative care is defined as focused on pain and symptom management with the incorporation of psychosocial and non-traditional healthcare needs. Within Patient Care Perspectives, these terms are further described for better contextual understanding
- Validated instruments or questionnaires to measure quality of life or broader patient reported outcomes, including symptoms, have been recently routinely incorporated in clinical trials and population based real world studies. These tools evaluate the patient perspective and the impact of the disease or intervention on subjective or humanistic outcomes. These instruments have helped to provide a comprehensive evidence-based profile at the broader mBC patient population level beyond just objective measures or outcomes
- In this report, quality of life and daily living qualitatively in patients with mBC is discussed mainly at the individual patient level as a self-reported metric in real world clinical practice and may not always align with the multidimensional definition of health related quality of life (HRQoL) reported in the literature or as assessed by many existing validated HRQoL instruments. The discussion incorporates feedback from patients outside clinical studies and considers a broad spectrum of influencing factors, such as depression, social isolation, pain, deterioration in sexual functioning and poor access to mental health services. This report supports the development of tools for assessing the impact of the disease and/or treatment at the individual patient level in clinical practice to personalize therapy and also help in the long term in improving overall outcomes at the broader patient population level



Section 1

Patient Care Perspectives



Introduction

// Balance, in the world of breast cancer metastasis for a woman who is going through the experience of the recurring disease, is essential for her survival. She must find the inner and outer resources to meet the challenges of her situation, to regain control, to harness her fears, to cope, to strive for normality and create stability and continuity. //

Evi Papadopoulos, Vice President of Europa Donna, 2015

Early breast cancer (eBC) has benefited significantly from advances in care over the past decade. (American Cancer Society Facts and Figures, 2014) While there have been efforts to advance the approach to management of metastatic breast cancer (mBC), there remains considerable room for improving patient care and support to patients and their families and caregivers. The mBC patient care needs evolve along the disease continuum, from the time of diagnosis to end-of-life care.

The course of mBC can be varied; some patients may live for several years with mBC, some may have a shorter continuum. Consequently, a patient's needs and experiences with the disease are diverse and very personal to each individual. However, there are some commonalities, which are highlighted throughout this section.

Throughout the disease continuum, patients tend to face highs and lows associated with both the disease and its treatment (Figure 1.1). The diagnosis of mBC represents a time of shock, crisis, and anxiety for patients and their families, and as such, they require sensitivity, as well as emotional and physical support. (Secondary Breast Cancer Taskforce, 2008)



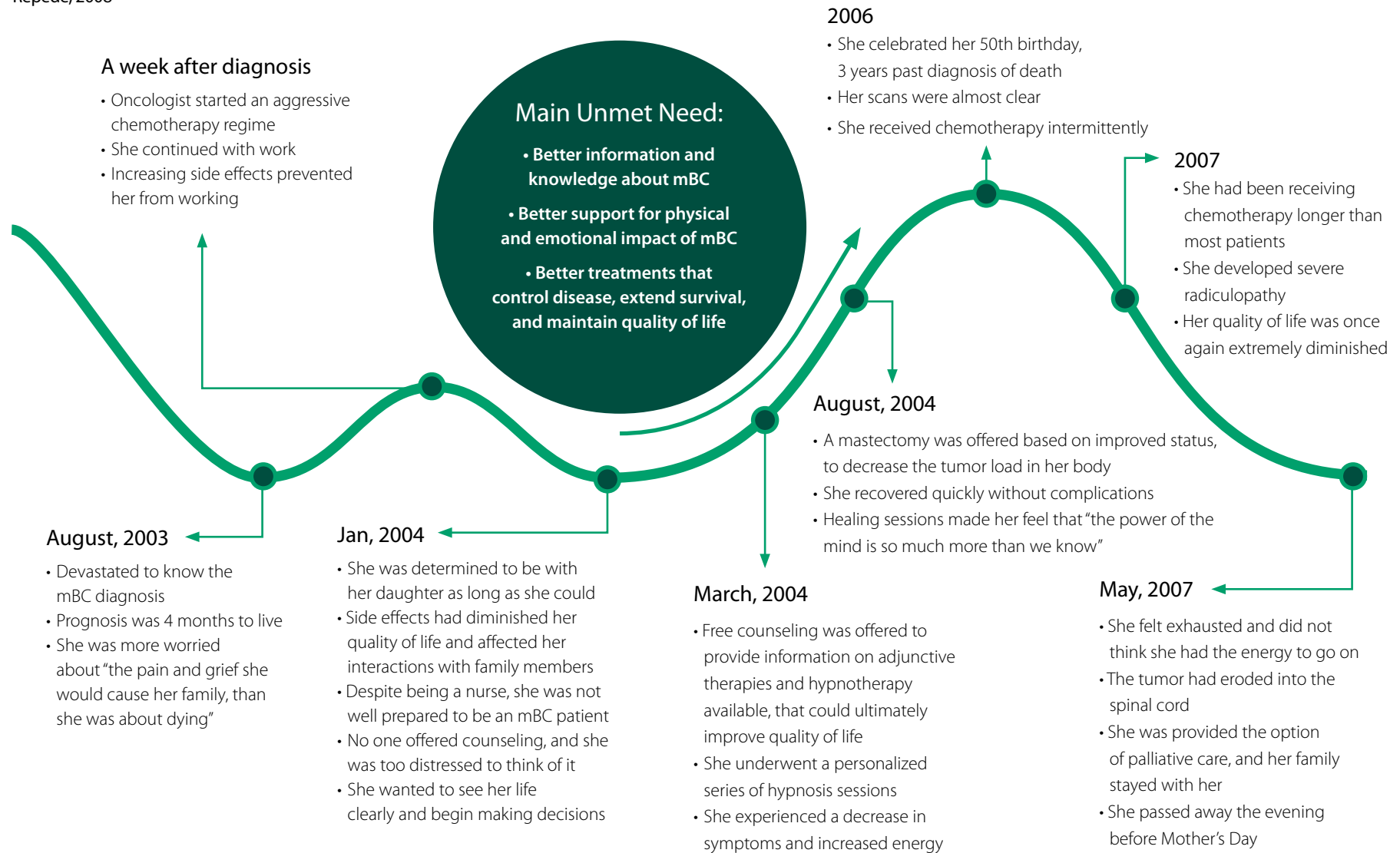
Cece Curry, mBC patient. Deceased June 2013



Figure 1.1

Highs and Lows of the mBC Patient Experience

Based on personal journal notes from a 47-year-old female, US, nurse with mBC
Repede, 2008



To better understand the current landscape and identify areas of focus moving forward, this section outlines the mBC patient's care needs along the disease continuum and the extent to which they have been addressed over the past decade.

Research has been conducted to better understand patient care perspectives in mBC. Reports generated from that research, such as the mBC Alliance Report (2014), highlight some existing fundamental gaps that were uncovered previously in the BRIDGE survey (2009). A multitude of factors were noted as important considerations for patients with mBC, these include: psychosocial well-being, quality of life, patient/caregiver needs and support requirements, and the overall burden that mBC places on patients and their families. The majority of documented strategies for the management of mBC are the result of efforts in the developed world; unfortunately, there is a scarcity of research from the developing world in mBC. However, globally, it is noted that there is both a lack of evidence at particular stages across the disease continuum and an inconsistency in the reporting of supportive care in mBC.

Methodology: To assess the complete body of evidence in relation to patient care perspectives after a diagnosis of mBC, a systematic literature review was conducted in EMBASE. One hundred and thirty two articles published from 2004-2015 were identified and reviewed. Details of key terms and search strategies are included in Section 1 Appendices and References. In addition to the systematic literature review, industry-sponsored or public studies not published in journals (ie, as surveys, reports, or white papers) were included in this review.

Also, a survey was conducted to understand insights related to management and support of mBC patients and healthcare professional perceptions of mBC patients' needs and perspectives. A total of 582 specialists were surveyed, respondents were those who treat breast cancer in cancer centers including: oncologists, gynecologists (Germany),

oncology nurses, and Breast Cancer Center leaders (C-Level, administrator, medical director of oncology). The 9 participating countries were: US, Sweden, Germany, UK, Italy, Portugal, Brazil, Mexico, and Australia. In all countries respondents were invited to complete a 30 minute self-administered internet survey. Because of the small sample in Sweden (n=14), results were analyzed separately and included in open-end reporting only.

Finally, in-depth interviews were conducted with 6 breast cancer centers from France, Argentina, Lebanon, India, and the United States to highlight diverse and unique approaches to managing and supporting mBC patients. These are included as breast cancer center profiles in this section.

A series of themes related to patient care perspectives were identified as a result of the literature search and primary research. These themes form the chapters of this section:

- **Information and Communication Needs**
- **Decision Making**
- **Quality of Life and Daily Living**
- **Supportive Care along the mBC Continuum**
- **End-of-Life Care**
- **Approaches to Delivering mBC Care: Cancer Center Profiles**

Quality of Life is a common theme discussed within this section.

While quality of life is most often described as a patient reported metric, captured using validated questionnaires and report data at a group level, this section refers to quality of life and daily living qualitatively for patients with mBC. It considers all aspects that could impact quality of life qualitatively and could apply at an individual patient level or represent general opinions.



Chapter 1: Information and Communication Needs

- Patients recognize the quality of information provided at an initial diagnosis of eBC but do not feel that this is matched at the point of diagnosis of mBC
- The breast cancer community has identified the need for holistic, individualized communication about mBC
 - Patients report inadequate communication and understanding about prognosis, treatment risks vs benefits, and future options
 - There remains a need for greater sensitivity and transparency from healthcare professionals
- There is a need for better information and proactive communication to patients about clinical trial options
 - Current information provided about clinical trials in mBC is variable and may either confuse or overwhelm patients
 - There is a need to address patient misperceptions about clinical trials
- Appropriate management of patients with mBC must be cognizant of cultural sensitivities

// The mental demands facing metastatic patients are significant. Our need for support and encouragement never ends because we will always be in treatment. //

Shirley Mertz, President, Metastatic Breast Cancer Network, 2015



A Patients have highlighted the need for greater mBC focused information

In a report exploring the individual experiences of women with mBC, it was highlighted that the information and support provided to them is inadequate compared to the services available at the time of an initial diagnosis of eBC. (Johnston, 2010)

Generationally, in a UK study, younger women were found to be less satisfied with the information and advice they received. Overall, these women highlighted dissatisfaction with the provision of information and support from healthcare professionals when compared with their experience of being diagnosed with early stage disease. (Reed, J Pain Symptom, 2012) Similar unmet needs were identified by women in Hong Kong with mBC (53% were diagnosed with mBC and the remainder with stage III disease) in a study conducted between 2008 and 2010. (Au, 2013) These examples highlight that within some areas of the world, there is a need for greater emphasis on provision of information for patients whose disease has progressed from eBC to mBC.

Healthcare providers also experience difficulties in providing patients with appropriate mBC-focused information. In a 2015 primary research survey conducted among specialists who treat breast cancer, 7 mBC-specific, patient-directed resources were considered helpful in greater than 62% of respondents. These resources included: identification of currently available resources for mBC patients and guiding patients to these resources; goal setting and potential questions for mBC patients and families/caregivers to ask their physician; referral to peer support and/or specific consumer organizations to support mBC patients; a patient/caregiver empowering guide outlining expectations for their mBC experiences; a conversation guide that patients can share with

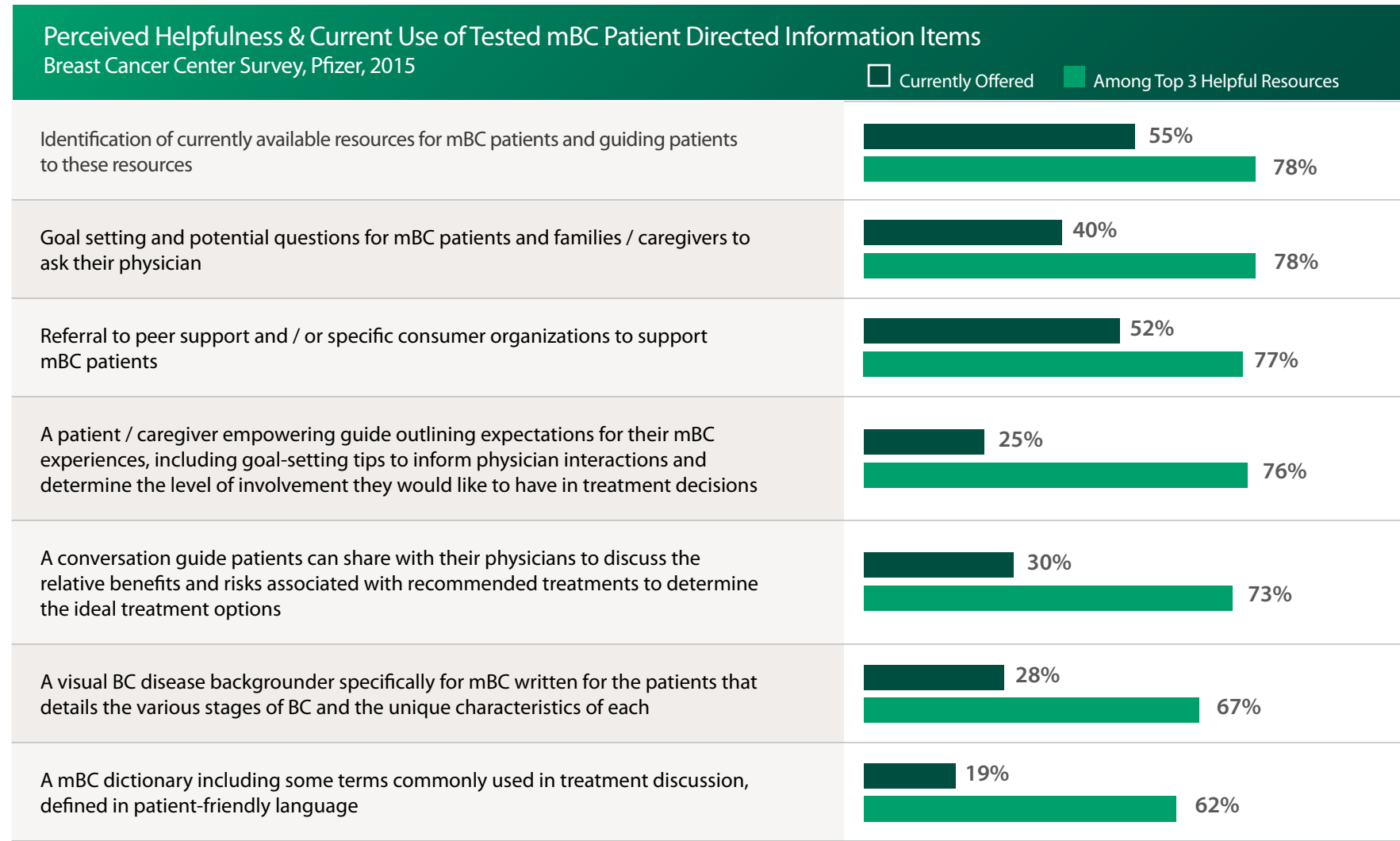
their physicians to discuss the relative benefits and risks associated with recommended treatments to determine the ideal treatment options; a visual BC disease backgrounder specifically for mBC written for the patient that details the various stages of BC and the unique characteristics of each; and an mBC dictionary including some terms commonly used in treatment discussions, defined in patient-friendly language. However, the same specialists frequently did not have these resources available to offer to their patients, as illustrated in Figure 1.2. (Breast Cancer Center Survey, Pfizer, 2015) Comparably, in an Austrian survey, physicians knowledgeable in metastatic cancers recognized that information about diagnosis and treatment may not be uniformly provided to patients at time of diagnosis. (Kierner, 2010)

Apart from information from their healthcare providers, there also needs to be adequate mBC focused information available for patients through patient support groups as well as internet based resources. In a study across 13 countries surveying 1,342 women with mBC, 46% identified patient support groups as an information resource; however, only 13% considered this the most useful source of information other than healthcare professionals, with 23% choosing a website or internet resources as the most useful sources of information. (Mayer, 2010)

Despite seeking information on a variety of topics about treatment and care from multiple sources, patients have difficulty finding the information they needed. Patients have specifically expressed a need for more information about future medical treatments, research and information on the balance between the benefits of treatment and the risks. (Harding, 2013) Despite the numerous channels through which information is disseminated, many breast cancer patients reported that they could not find ongoing community or internet-based educational programs. (LBBC, 2015; Nahleh, 2013)



Figure 1.2



BCC Quant July 21-Aug 12, 2015

Q41, Q42 Base = Total Respondents (n=568)

Q41, How helpful to your *mBC patients and their families / caregivers would each of the following be? 1 = Not Helpful at All, 7 = Very Helpful

Q42 Please indicate if you currently offer each.

*Stage IV / Unresectable Advanced BC

Respondents were from US, UK, Germany, Italy, Portugal, Brazil, Mexico, and Australia



B Women with mBC have identified the need for holistic, individualized, and compassionate communication about mBC from their healthcare professionals

Honest communication about prognosis and anticipated treatment benefits, which is delivered with empathy and compassion by healthcare professionals, is anticipated to allow a patient to maintain hope while also being realistic about the likely outcome. (Grunfeld, 2006). In a study performed with 126 patients in Australia with metastatic diseases, it was found that a majority of patients preferred realistic, individualized approaches from the healthcare professional, including details about prognosis and progression. (Hagerty, 2005) When communicated sensitively to the patient, it empowers them to participate fully in decision making for their care. (Cleary, 2013) Further, patients then have the option to access a spectrum of supportive, palliative, end-of-life, and survivorship care services, where these services exist.

Misperceptions about mBC exist and the incurable nature of mBC may not be recognized by patients. According to nurses and physicians interviewed for the 2015 Global Cancer Center Survey, the most common misconceptions that patients with mBC experience are that pain is inevitable and uncontrollable, no effective treatments are available, and a cure is still possible. (Breast Cancer Center Survey, Pfizer, 2015) Patients should be informed that there may be multiple treatment options remaining, support is available, the disease is treatable even though incurable, treatment can maintain quality of life, and they will continue to receive the best care. (Breast Cancer Center Survey, Pfizer, 2015)

However, an in-office ethnographic survey conducted in 2014 observing the interactions between 22 US mBC patients and their oncologists uncovered that the severity of metastatic disease tends to be minimized by physicians. In conversations studied, metastatic disease was conveyed as a chronic, livable disease, which minimized the actual severity of mBC.

As a result, prognostic information was unclear, and patients were not being provided the maximum opportunity to plan accordingly. (A Story Half Told, Pfizer, 2014)

While providing adequate information to patients about their illness and care is important, healthcare professionals must also remain sensitive to the patient's individual preferences. While some patients with mBC may want full disclosure of prognosis information, others may prefer less information on their prognosis in order to try to maintain feelings of hope. As such, comprehensive standardized support packages may not be optimal for all patients with mBC, suggesting the need for a more tailored approach. (Grunfeld, 2006) A customized approach to information provision was implemented in patients in Hungary with both eBC and mBC, resulting in a meaningful decrease in reported anxiety levels. Distress levels were decreased by providing patients with as much information and involvement in decision-making regarding therapy as they were comfortable doing. (Kahán, 2006)

Quality of life issues should also be discussed, along with tools for communicating and sharing their experiences more successfully, with family, friends, and their community. (Mayer, 2010; Nahleh, 2013) Half of patients/caregivers also felt care could be enhanced if healthcare professionals listened more to patients, ensured continuity of care with the same doctors, nurses, and specialists (55%), and guaranteed the availability of counseling, if needed (55%). (Harding, 2013)

In one study, nearly 40% of patients expressed a need for greater sympathy and/or empathy from healthcare professionals.

(Harding, 2013)



Only 43% of healthcare professionals report having received training on how to bring bad news to patients and families.

(Breast Cancer Center Survey, Pfizer, 2015)

An open and honest discussion about mBC prognosis needs to incorporate greater sensitivity and empathy. In one study, nearly 40% of patients also expressed a need for greater sympathy and/or empathy from healthcare professionals. (Harding, 2013)

Feelings of blame and regret experienced by women with mBC, along with questioning if their disease was being managed correctly, can complicate the intricate and sensitive nature of the disease. As a result, increased communication difficulties were experienced between the patient and physician. (Danesh, 2014) Healthcare professionals find talking about prognosis difficult and feel that their training could be improved to allow effective communication about end-of-life issues. (Cleary, 2013) Access to physician training and information on how to conduct discussions and respond to questions about prognosis and end-of-life matters, may be beneficial to help address some of these challenges. (Danesh, 2014) However, evidence from a 2015 primary research survey,

commissioned by Pfizer, suggests that healthcare-professional training and information is often unavailable. Although 83% of respondents identified “learning how to bring bad news to patients and families” as a key training need, only 43% had received this level of training. (Breast Cancer Center Survey, Pfizer, 2015)

Healthcare professionals should be educated about effective patient communication through training programs, should be culturally sensitive, and recognize that patient educational needs may differ based on age, ethnic background, religion, and nationality.

🕒 There is a need for better information and proactive communication to patients about clinical trial options

Clinical trials are an important component to both treatment and maintenance of hope for patients with mBC. Women who seek out information about their disease have been found to be more likely to be actively involved in their therapy decisions and to participate in clinical trials. (Mayer, 2010) In order to support healthcare professionals and patients with the delivery of evidence-based medicine in oncology, a sufficient number of clinical trials must be ongoing to continually generate new data and treatment modalities. (Cardoso, 2011) Poor recruitment into clinical trials for mBC is an issue, (Nahleh, 2013) which underscores the importance of appropriate communication between

“ Even the way researchers and healthcare providers sometimes say, “The patient failed treatment X” suggests that the patient somehow fell short. But it is really the therapy that failed the patient. ”

Kimberly Sabelko, PhD, Managing Director, Strategic Partnerships and Programs, Susan G. Komen, 2015



patients and healthcare professionals about the availability of clinical trials and the benefit of participation. In fact, a 2015 US study found an association between clinical trial participation and increased overall survival (OS), particularly with certain subsets of mBC. (Kim, 2015) These results suggest there is a need to change the perception, for both healthcare professionals and patients, that clinical trials are a “last resort.” In a 2015 call to empower patients as the driving force behind drug development, Richard Pazdur, Director of Office of Hematology and Oncology Products at the FDA, highlighted the need to look again at eligibility criteria and the informed consent process in clinical trials. (Sutter, 2015)

One misconception is that clinical trials in oncology provide an option of “last hope”; instead they should be perceived as a potential augmentation to the standard of care for mBC. (Nahleh, 2013) Of those patients participating in a clinical trial, the main reason identified for doing so was encouragement by a healthcare professional. (StatBite, 2009) However, 78% of patients with mBC report they had never participated in a clinical trial and cite never having been invited or receiving a recommendation from the healthcare provider as the reasons. (Statbite, 2009)

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There are a number of potential explanations for this lack of communication by healthcare providers. Financial disincentives exist for

clinicians in non-trial centers to refer patients to another treatment center offering access to trials. Furthermore, exclusion criteria may reduce the eligible population by prohibiting the enrollment of an individual due to factors such as age, stage of disease, treatments already received or presence of concurrent illness, which may prevent discussion about the opportunity. (Institute of Medicine US Forum on Drug Development, 2010)

When clinical trial information is presented, its content may vary greatly and can confuse or overwhelm even well-educated patients. Where knowledge about the opportunity for clinical trial entry exists, oncology patients fear being entered into a placebo arm, despite there being an ethical requirement that patients in cancer trials must at least receive standard of care. In their minds, the placebo arm would be the same as receiving no treatment. Effective communication by healthcare professionals is necessary to correct this point or challenge the perception that entry into clinical trials is a last resort. (Institute of Medicine US Forum on Drug Development, 2010)

To address this, a number of clinical trials now utilize new approaches (such as interactive DVDs, web-based approaches, short informational decision aids) that may aid patients in better understanding the trial's objectives. (Nahleh, 2013) In addition to online resources, it is also important to have paper-based clinical trial information available for patients with mBC who have no internet access. (Harding, 2013; Boonzaier, 2010)

Beyond the need for improved communication, increasing education of healthcare professionals would help ensure they can thoughtfully encourage patients to enter into trials. Education and engagement should not be limited to physicians but should also include nurses and other healthcare providers who play a vital role in treatment and are an invaluable source of information. Defining the roles of physicians and nurses in clinical trial discussions may also facilitate greater healthcare professional and patient discussion. (Nahleh, 2013) Resources to assist



patients in identifying all available clinical trials outside of the traditional healthcare setting may also facilitate future discussions regarding clinical trials between patients and their healthcare providers.

D Appropriate management of patients with mBC must take into account cultural sensitivities

All approaches to improving the patient care pathway for women with mBC should take into consideration cultural and religious influences on patient behavior. Cultural differences may alter information preferences of patients with mBC. While many cancer patients in Western countries (up to 85%) state that they want all information, positive or negative, a minority prefer to receive minimal information only. Across the world, religious differences may influence how much information the patient would like to know vs leaving decisions to a higher power. (Butow, 1997; Banning, 2014) In many developing countries, the majority of patients are initially diagnosed with mBC (rather than eBC), which often leads to poor outcomes and its associated burdens. (Pakseresht, 2014; Anderson, 2006; Bhatt, 2011)

Furthermore, ethnic and language diversities can bring additional challenges. For instance, in some indigenous African languages there is often no adequate synonym for the word “cancer”. (Maree, 2010) In such cases, translation of health promotion materials to ensure correct interpretation by the target audience becomes more difficult.

Around the world, breast cancer nurses already perform a key role in educating women with mBC and providing support for patients and their families. It is therefore vital that all healthcare professionals are adequately trained, supervised, and coached to be able to provide patient support in a multitude of different societies and cultures. Holistic care is particularly important in cultures where patients rely on religion as a coping mechanism. (Banning, 2012) It is important that nurses and healthcare professionals, whether members of those cultures or not, are aware of the cultural needs and sensitivities of their patients with mBC to ensure optimal care for all cultural backgrounds. This may require the recognition of a family-centered model of decision making, rather than an individual-autonomy model, within some cultural groups. It is critical that healthcare professionals and other support staff acknowledge and are sensitive to cultural beliefs of women with mBC and their families.



Chapter 2: Decision Making

- Patients with mBC face more complex decisions regarding their care as they live longer and have more treatment choices
 - There is a need to recognize the increasing complexities in balancing multiple goals of managing mBC
 - A sound relationship between physicians and patients is needed to facilitate joint decision making
- Some progress has been made in joint decision-making between patients and their physicians, but much more needs to be done
 - Some countries offer guidelines and information on advanced care planning
 - There is a need for greater emphasis on finding opportunities for patients to share their treatment goals with their physicians
 - Treatment decision making should avoid discrimination against older patients with mBC

A Women with mBC face increasingly complex decisions regarding their care, including treatment goals and preferences

In the past decade, there have been modest improvements in median survival of patients with mBC, caused primarily by increased understanding of the disease and advances in mBC treatments. (Ruiterkamp, 2011; Barinoff, 2013; Rossi, 2013) As women live longer with mBC, they now face more complex decisions regarding their care because of this change. These decisions are often time-sensitive and must balance personal therapeutic goals, drug toxicities, quality of life, and the reality of uncertain outcomes. Women with mBC can experience feelings of confusion and conflict when facing treatment decisions. (Danesh, 2014) Ultimately, the final decision regarding treatment should be a joint decision made by the patient and the physician. This relies on establishing a sound relationship between the physician and the patient from the beginning. (Filleron, 2015) However, the extent to which patients are involved in the decision-making process should

be in line with their actual desire for participation. (Grunfeld, 2006) The MBCAlliance is undertaking a program of research to identify and design tools that remove the communication barriers between patients and their healthcare providers. This will allow patients to easily access information that will support their informed decision-making. (MBCAlliance, Communication Tool, 2015) Separately, work has been done which shows that the use of apps can be an acceptable and effective approach to patient education about treatments. (Younus, 2015)

Understanding patient preferences and goals are vital in making treatment decisions, comparing therapies that have different side-effect profiles, determining the aggressiveness of the treatment strategy and deciding when to switch from active treatment to palliative care. (Sepucha, 2009; mBC in Canada, 2013) In order to play an active role in decision making, patients need to be accurately informed about their diagnosis, prognosis, and treatment options. (Chiew, 2008) Use of simple calculations based on median overall survival to create best case, worst case and typical scenarios have been shown to help patients with mBC understand



survival data. (Vasista, 2015) Adjustment and acceptance of a diagnosis of mBC takes time, and so discussions about treatment goals should be revisited along the continuum of the disease course. As treatment options change, patients should continually be asked about their treatment goals so that their healthcare providers are clear about their wishes. It can be emotionally challenging for both patients and healthcare professionals alike to stop active treatment and acknowledge there may be little chance of prolonging life or palliating symptoms with further anticancer therapy. (Sepucha, 2009)

As more mBC treatments have been approved over the last decade, and as additional treatments may become available in the future, the complexity of making treatment choices will continue to increase. When making treatment decisions, a US survey found that the likelihood of treatment benefit was more important than toxicity when considering common treatment options for mBC (patients would opt to undergo a treatment with 27%-33% likelihood of benefit regardless of the toxicity scenario presented). (Smith, 2014) Patients indicated a willingness to endure side effects and delay or eliminate aspects of their life for a treatment that “is working” (ie, one that extends overall survival or progression free survival).

In evaluating treatments, the majority of patients (63%) from a study of 282 US mBC patients indicated they preferred treatments with longer disease control. Longer disease control was also associated with better emotional well-being (58%), higher overall quality of life (41%), and better physical functioning (31%). (Hurvitz, 2013) In a European study of patients with metastatic or locally advanced breast cancer, survival was indicated as the priority for the majority of women, with patients being willing to “trade-off” drug side effects in order to prolong their life (6% of respondents were caregivers). (Harding, 2013)

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B Progress has been made in joint decision-making between patients and their physicians, but much more needs to be done

In the United States, the Centers for Disease Control and Prevention (CDC) offers guidelines and information on advanced care planning for all patients. The goal of these guidelines is to ensure patients understand their choices in care decisions both before and during illness, and even at end-of-life. Ultimately, it is important the patients decide what they want based on their definition of quality of life. (Tangum and Benson, 2012)

After a 3-month use of decision aids, agreement between patients and providers on the main goal of treatment (ie, lengthen life vs relieve symptoms) improved from 50%-74%. (Sepucha, 2009)



In a US survey, the use of decision aids was found to be beneficial for patients and did not increase patient distress. The majority of patients desired to share decision making with their doctor, however only 38% achieved their desired level of participation. After a 3 month use of decision aids, agreement between patients and providers on the main goal of treatment (ie, lengthen life vs relieve symptoms) improved from 50%-74%. (Sepucha, 2009)

Approximately half (56%) of patients will always or usually voice their treatment aims, whether unprompted or in response to a direct question from their doctor.

(Breast Cancer Center Survey, Pfizer, 2015)

In an ongoing US study, the use of a continuing medical education tool by health care providers and patients is being assessed to show its impact on adherence to nationally recognised treatment guidelines to improve supportive care. (Hathaway, 2015)

In a survey of 582 physicians, nurses, and breast cancer center leaders, it was found that it takes, on average, 3 discussions with their oncologists before patients with mBC have a clear understanding of the goals of their therapy. However, only about half (56%) of patients are likely to voice their treatment goals, whether unprompted or in response to a direct question from their doctor. This data shows that there needs to be a greater emphasis on finding opportunities for patients to communicate their treatment goals with their healthcare providers and for clinicians to ask more probing questions. (Breast Cancer Center Survey, Pfizer, 2015)

According to healthcare professionals, on average, it takes 3 discussions with their oncologists before patients with mBC have a clear understanding of the goals of therapy.

(Breast Cancer Center Survey, Pfizer, 2015)

Treatment decision making should avoid discrimination against

older patients with mBC. In order to increase collective decision making between physicians and older patients, and to ensure treatment decisions are not defined by patient age alone, treatment options need to be tailored for older patients with mBC. (Freyer, 2006) Age has been found to be a discriminating factor in treatment decisions, with patients older than 76.5 years old being treated in a different way in comparison to younger patients. Elderly patients are often treated with weaker doses of chemotherapy, which is often based on a subjective evaluation of the patient's general health status. Available data indicates that a different approach in older patients with mBC is justified. (Hamberg, 2007) Physicians treating mBC may benefit from collaboration with a geriatrician or, alternatively, specific training of all physicians in the field of geronto-oncology. (Freyer, 2006)

Treatment decision making should avoid discrimination against older patients with mBC.

(Freyer, 2006)



Chapter 3: Quality of Life and Daily Living

- Women with mBC experience a decline in their quality of life and daily living
 - A desire for maintaining quality of life is often expressed by patients and physicians
 - Evidence suggests patient quality of life scores, after a diagnosis of mBC, may not always improve
 - There is a need to improve how we assess quality of life in patients with mBC
- Being diagnosed, then living with mBC greatly impacts patients' emotional and physical well-being
 - Distress, depression, and anxiety weigh heavily on mBC patients' emotional state
 - Patients also experience social isolation, feelings of reduced self-worth, pain, and sexual dysfunction
- Caregivers and healthcare professionals are directly affected by the impact of caring for a patient with mBC, but do not receive adequate support
 - Family-focused interventions may help patients and caregivers to cope with cancer together

“ Living with mBC is like walking on a tight rope, a balancing act using all resources, to hold on and reach the other end. ”

Evi Papadopoulos, Vice President of Europa Donna, 2015



The burden of mBC is significant and can be felt particularly around the time of diagnosis and as patients near the end of their lives. A patient's overall well-being is impacted by a number of factors associated with their disease, such as physical burden, psychosocial burden, caregiver burden, and financial burden. A patient's overall well-being, sometimes referred to as quality of life (QoL), is often impacted by both internal and external factors. Further, each of these factors can be additionally complicated by cultural sensitivities. Here, quality of life has been defined through instruments used in clinical studies as well as from multiple patient research and primary surveys conducted.

There are a multitude of factors related to the burden associated with mBC, from the physical and psychosocial impact on the patient to the burden on both caregivers, and healthcare professionals.

A Women with mBC experience a decline in their quality of life and activities of daily living

The overall burden facing women with mBC can be reliably assessed using quality of life analyses. As mentioned previously, patient quality of life is impacted by a number of factors that include, but are not limited to, physical burden, psychosocial burden, caregiver burden, and financial burden. It is important to note that each individual patient's values will directly impact their assessment of quality of life.

Eight out of ten women feel that quality of life is the biggest area in need of improvement in mBC care. (Here & Now, Novartis, 2013) Fatigue, insomnia, concentration, neuropathy, and pain are consistently mentioned by patients as having the greatest effects on their quality of life. (mBC in Canada, 2013; Danesh, 2014) While quality of life is being frequently touched upon in consultations, it is often quickly and vaguely discussed, therefore leaving women feeling as though their needs have not been met. (Danesh, 2014)

Patient quality of life is impacted by a number of factors that include, but are not limited to, physical burden, psychosocial burden, caregiver burden, and financial burden.

(Here & Now, Novartis, 2013)

The ability to accurately quantify changes in quality of life amongst patients with mBC remains challenging. Quality of life is referred to in many quantitative and qualitative patient care perspective surveys. However, there is no standard definition of quality of life in clinical practice at the individual patient level, and variation exists in how surveys/studies report on this measure across the general patient population. Patients and physicians often express the explicit hope to maintain "quality of life" without further explanation or definition of its meaning. (Danesh, 2014) Standardized and validated instruments for measuring quality of life in clinical trials exist, but are not used in clinical practice. (FACIT.org; EORTC.org; Osoba, 2011) Without better understanding of what quality of life should mean as both a standard and at the individual level, it is nearly impossible to ensure that patients' unmet needs regarding quality of life are being addressed in real world clinical practice. A more structured definition of quality of life is needed, both for patients to verbalize their needs and also to support the broader community.

Eight out of ten women feel that quality of life is the biggest area in need of improvement in mBC care.

(Here & Now, Novartis, 2013)



Methodology: A review of mBC related quality of life studies/surveys was conducted and established that data published on QoL instruments are commonly used in clinical studies, but the same does not seem to be true of the real world clinical practice setting. A description of the approach taken is provided in Section 1: Appendix 1.3.

In some cases, general noncancer-specific QoL instruments are being utilized, such as the EQ-5D, 12-Item Short Form Health Survey (SF-12), and 36-Item Short Form Health Survey (SF-36). These instruments are patient-reported surveys of general health status. (Perrillon, 2015) Some cancer-specific QoL instruments were also used, with the EORTC core QoL questionnaire (QLQ-C30) and Functional Assessment of Cancer Therapy Questionnaire (FACT-G) being examples. For both instruments, a breast cancer-specific questionnaire does exist, ie, the EORTC breast cancer-specific QoL questionnaire (EORTC QLQ-BR23) and FACT-B (for patients with breast cancer).

Questionnaires to assess the value of delaying progression in mBC need to be developed. (Perry, 2007) However, pilot studies have begun evaluating mBC-specific questionnaires. (Hurvitz, 2013)

Questionnaires to assess the value of delaying progression in mBC need to be developed, suggesting that current methods to capture this measure are not fully capturing patient experience. (Perry, 2007) However, pilot studies have begun evaluating mBC-specific questionnaires, for example mBC-P. (Hurvitz, 2013)



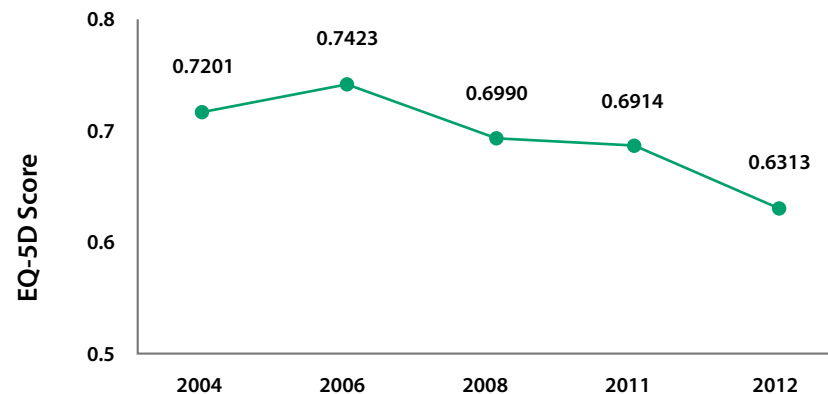
Methodology: Due to different quality of life measures used in clinical studies, it is difficult to assess how quality of life has changed over the past 10 years. As such, an analysis was conducted to convert quality of life measures to EQ-5D in order for us to understand trends in quality of life over the past 10 years. Please see Section 1: Appendix 1.3 for detailed methodology.

Quality of life for patients with mBC has not improved in the last decade. A review of the trends in quality of life for mBC within this analysis indicates that there has not been a significant improvement in patients' quality of life since 2004 (see Appendix 1.3 for methodology). In fact, there has been a slight drop in measured quality of life over these years (see Figure 1.3).

Figure 1.3

Quality of Life in Patients with mBC as Assessed by EQ-5D, 2004-2012, Generic (non-Cancer Specific) Health Utility Score

Research from Appendix 1.3



Analysis was based on a review of 132 articles, of which a quantitative analysis was conducted of 14 studies reporting QoL measure values for mBC. Values are weighted based on sample size.

This analysis indicates a numerical decrease over time. It does not intend to demonstrate statistical significance.

Why has there been a reduction in overall quality of life in patients with mBC since 2004, despite advancements in treatment during that time? What if treatments reduce quality of life? The lack of improvement observed in quality of life for patients with mBC may be underscored by a failure to address remaining unmet needs. More research is required to determine what approaches create the greatest benefit in resolving their quality of life concerns, for example access to referral services. (Mosher, 2013) While there are numerous treatments available for mBC and more in development, they may not be able to address the myriad of factors that potentially impact a patient's quality of life, including physical side effects and emotional well-being in patients with mBC. Lastly, as mentioned previously, these results may not accurately reflect quality of life due to the use of nonspecific instruments.

Further development of mBC-specific QoL instruments, for both clinical trial and community use, is essential to improve our understanding of this measure in patients with mBC and assess quality of life in association with any new intervention, as well as for flagging potential unmet needs in this specific group of patients. There is clearly an opportunity to improve quality of life for these patients, and more accurate assessments will allow for targeted solutions.

B Being diagnosed and living with mBC greatly impacts patients' emotional and physical well-being

Emotional functioning is a key indicator of quality of life for patients with mBC. Patients report feeling bad-tempered, down, depressed, and less tolerant. Some feel bitter and find it very difficult to accept their fate,

while others describe anger as the most predominant feeling. Physical and emotional functioning are intertwined where days without pain, fatigue, insomnia, or vomiting can be indicative of a positive mood. Patients closely associate their emotional functioning with the ability to enjoy life, giving them the strength to commit themselves to treatment. Often patients' coping methods rely on denial and avoiding thinking about their illness in order to sustain their emotional functioning and live a somewhat normal life. (Luoma, 2004; Danesh, 2014; Aranda, 2005) For most women, their disease strengthened their religious beliefs, and through their religion, they became emotionally stronger. This reinforced faith provided a personal coping strategy which enabled women to manage their illness and improved their overall sense of well-being. (Banning, 2014)

In a US-based study, women reported struggling to accept a diagnosis of mBC, which manifested into feelings of blame or regret. (Danesh, 2014) Feeling scared, confused, depressed, angry, and alone at the time of diagnosis was observed in 55%-80% of women in a survey of patients with mBC between 2008 and 2009, across 13 countries. (Mayer, 2010) Physicians suggest disappointment or distress at progression to mBC was associated with a number of feelings. (Wardley, 2008)

In a study of 282 women with mBC, patient's emotional well-being after a diagnosis of mBC (new to breast cancer, or progression from earlier stage disease) was found to be worse than in those given a diagnosis of eBC. Younger (< 50 years) and newly diagnosed women indicated their emotional well-being was more negatively impacted than women who were either older or had lived with mBC for some time. (Hurvitz, 2013)



This highlights a greater emotional need for patients at initial diagnosis of mBC, which may require a more intensive level of support. Further, women at a younger age may also require more intensive supportive services given their stage of life and the perception of greater life expectancy generally.

Figure 1.4

Common Words Signifying Patient Experiences Throughout mBC Diagnosis and Treatment

Wardley, 2008; Danesh, 2014; Luoma, 2004; Aranda, 2005



In many countries, patient groups exist to help women discuss their diagnoses, share their experiences and seek support from one another. While this type of psychosocial support does not have any effect on disease outcome, it does improve mood and the perception of pain, particularly

// I did everything right, I did everything the doctor told me to do, and look what happened anyway... It's the same thing that makes people fear metastasis and recurrence. You don't know what causes it, and you know it could happen to you. Your logical brain knows, but you still feel that somehow your body betrayed you. I've heard it over and over again. Many times people have been told they've been cured, and then become metastatic—and that's a horrible thing. //

*North American Respondent,
mBC PSO Survey, Pfizer, 2015*

in women who are initially more distressed. (Goodwin, 2001) A pilot study has indicated that provision of preparatory information at the time of diagnosis may enhance patients' coping ability and also assist in managing expectations around the disease; such tools require further investigation to validate their usefulness in relieving burden at diagnosis. (Rosenzweig, 2010)



If not addressed early, manageable emotional burdens can quickly escalate; 61% of women in one study were identified as distressed and one week later, they reported clinically significant anxiety or depressive symptoms. (Mosher, 2012)

Distress, depression, and anxiety weigh heavily on mBC patients' emotional well-being. Depressed mood may interfere with a patient's coping mechanisms, or even compliance with treatment regimens, (Kissane, 2004) making it an important area for clinicians to address with patients. In 2008, a study among patients with mBC in the Czech Republic found the incidence of depression to be 61%. 20% of the 25 patients diagnosed with mBC had severe depression, 40% were moderately depressed, and 40% had mild depression. Overall, there was found to be an association between mBC, depression, and the low level of global quality of life. (Slovacek, 2010)

If not addressed early, manageable emotional burdens can quickly escalate; 61% of women in one study were identified as distressed (using a screening instrument) and one week later, they reported clinically significant anxiety or depressive symptoms. The majority of patients (70%) also suffered from sleep disturbances indicating that emotional burden can also impact sleep. (Mosher, 2012)

Women with mBC frequently experience a lack of self-identity and disruption to their family life. In a study of 25 women with mBC, it was found that those who work outside the home or have active professional lives were unable to continue their employment, were on prolonged sick leave, or forced to retire. Many women described themselves as feeling useless in society when they had to stay away from work (ie, on sick leave or disability pension).

A few patients who were still employed, emphasized how important it was to them to continue working to ensure that their lifestyle was altered as little as possible. Women who served important roles within their families also found themselves limited, as their ability to perform domestic work was also diminished. These limitations prevent women from maintaining their previous roles, and this change (from being needed, to needing someone) is difficult to accept, leading to a decreased sense of autonomy. (Luoma, 2004)

The consequences of an mBC diagnosis on family life have a significant impact on a woman's self-identity as mother and partner, particularly in families that include younger children.

// Although I stay as positive as possible, there is always the horrible doubt of "what if" and "when". //

mBC Patient, from Secondary Breast Cancer Research, BCNA, 2014

For example, detrimental effects on patient well-being occur when cancer affects social functioning, such as children choosing not to invite their friends over if their mother is experiencing side effects of treatment. Additionally, worries and concerns can arise about how a spouse or partner will cope with their disease or possible death. (Luoma, 2004; Mosher, 2013; Badr, 2010) This impact on self-identity might be a particular problem in cultures where women have the predominant responsibility for caring and bringing up children and can add considerable emotional burden at an already challenging time. (Banning, 2014)



Metastatic disease often results in social isolation. Social functioning in patients with mBC can deteriorate, along with confidence and comfort levels, with appearance changes due to treatment-related side effects (ie, alopecia). Patients may modify their behavior by staying at home to limit opportunities for socializing in their community, with friends, or in the workplace despite recognizing that they miss normal social interactions. Patients are concerned that wearing a wig makes their diagnosis obvious to strangers and symbolizes the loss of personal control over their cancer experience. (Luoma, 2004) For more information on caregivers and social relationships, please see Section 2, Chapter 6: *The Impact of mBC on Patient Social Relationships and Caregivers*.

Maintaining normal interpersonal relationships and being able to control the illness experience are crucial to patients' maintaining healthy emotional well-being. Activities that enable patients to lead a near normal life are helpful, particularly those that patients enjoyed before their diagnosis. Patients have observed that learning to live for the moment and learning new ways of enjoying things helped them to grow personally and in turn reduce their emotional burden. (Luoma, 2004)

Patients have observed that learning to live for the moment and learning new ways of enjoying things helped them to grow personally and in turn reduce their emotional burden. (Luoma, 2004)

Pain, fatigue, and weakness impacts patients' daily lives. A survey in Europe of 158 women with mBC and 146 caregivers, found that half of women experienced pain that interfered with their daily life and half suffered from discomfort and anxiety. (Here & Now, Novartis, 2013) Quality of sleep has also been found to be significantly decreased in patients with mBC; this may be due to increased pain. (Mystakidou, 2007)

mBC treatment can also result in fatigue and weakness, which limits the ability to conduct daily activities. That is not to say that all physical side effects related to treatment have a negative effect, some patients with treatment response experienced improvement in their physical condition as a result and thus felt joy. (Luoma, 2004)

// Family and friends find it extremely hard to understand the concept of Stage IV cancer, being incurable, and meaning that you have to be on treatment for the rest of your life. If you are on a treatment with no visible side effects, even the most intelligent and loving friends and family members don't really remember that you have cancer. //

mBC Patient, from Secondary Breast Cancer Research, BCNA, 2014



Deterioration in sexual function has far reaching physical and emotional impact. Sexual function is an area that receives very little attention and investigation in many diseases, including mBC. Despite a 2014 US study finding decreased sexual interest as one of the most severe symptoms of mBC, (Cleeland, 2014) limited research has been completed to study its impact. (Milbury 2013) Links between sexual problems, depressive symptoms, and types of spousal communication patterns have been identified, indicating that reduced sexual function may have broader implications. (Milbury, 2013) Sexual problems were associated with depressive symptoms in both patients and their partners. (Milbury, 2013)

Deterioration of sexual function has far greater consequences than physical function alone, as patients' emotional and social well-being are also impacted. Couple-based interventions that address patients' and partners' sexual concerns are beneficial to help alleviate depressive symptoms for both members of the couple. Teaching effective

Despite a 2014 US study finding decreased sexual interest as one of the most severe symptoms of mBC (Cleeland, 2014), limited research has been completed to study its impact. (Milbury 2013)

communication patterns, such as mutual engagement and joint problem-solving, is key to support improved emotional intimacy and sexual satisfaction. The role of communication is important in identifying and alleviating burden associated with sexual function. It may however require some nuances to be effective for both partners. (Milbury, 2013) Enhanced communication about sexuality may also help to support

broader improvements in psychological adjustment for patients with metastatic disease. (Au, 2013)

The lack of attention to sexual dysfunction in mBC patients is further compounded by cultural sensitivities around sexual function. In some cultures, discussing sexual concerns and satisfactions is highly sensitive; however, despite these sensitivities, avoidance is not the best solution. Facilitation of culturally sensitive interventions that support couples of all cultures could lead to better care of sexual function burdens and overall improved quality of life in women with mBC. (Au, 2013)



Debbie Gurley, mBC patient diagnosed in March 1998. Living with the disease.



“ Uncertainty... am I going to have enough money to see me out...how does all of this affect my standard of living and therefore my relationships with family and friends? ”

mBC Patient, from Secondary Breast Cancer Research, BCNA, 2014

Younger patients with mBC face challenges different to those of older patients due to diagnosis at an earlier stage of life.

Survival rates for young women (≤ 40 years of age) with breast cancer remain lower than those for older women, particularly because young women have an increased likelihood of developing more aggressive subtypes of breast cancer and presenting with more advanced stage disease. (Rosenberg, 2015) There are a variety of differences that affect the management of breast cancer for young women, including being premenopausal at diagnosis, fertility, genetics, and social/emotional issues with being younger at the time of diagnosis. (Rosenberg, 2015) Additionally, many younger women may experience sexual dysfunction, which arises during treatment and may only partially resolve after treatment has been completed. (Kedde, 2013) All of these aspects should be considered early in the course of care.

Younger age at diagnosis is associated with greater symptom severity and interferences, worse health-related quality of life (HRQoL), and greater activity impairment than experienced by older patients. (Cleeland, 2014)

Younger age at diagnosis is associated with greater symptom severity and interference, worse health-related quality of life (HRQoL), and greater

activity impairment than experienced by older patients. (Cleeland, 2014)

An mBC diagnosis at a young age is often accompanied by the realization that there is less time to experience aspects of life that were previously taken for granted, particularly the positives experiences of growing older. Will you live to see your children graduate college? Will you celebrate your 10th wedding anniversary? Additionally, end-of-life planning requires a high level of diligence because patients are often still working to support a family who will financially struggle when they are unable to work anymore. Generally, younger patients will assume more active roles either at home or by returning to work than older patients, (Cleeland, 2014) having then to deal with the challenge of supporting their families, as well as their own lifestyles while battling mBC.

Economic and family-life factors, specific to younger women, mean that

“ [In some African countries] the literature is focused almost entirely just on treatment with little discussion of patient quality of life or standard of practice. There is no explanation that breast cancer must be diagnosed, staged and properly treated. ”

Dr. Olufunmilayo Olopade, Director of the Center for Clinical Cancer Genetics, University of Chicago, 2015



a particular research focus is required for this population. Prioritization should focus on the effects of shared decision making, balancing body image, fear of recurrence, recommended treatments and lastly, palliative care. (Fernandes-Taylor, 2015)

The financial implications of mBC on women and their families can impact quality of life. While there have been relatively few articles published detailing the economic burden of mBC on patients, it is important to recognize the expensive nature of health and social care, particularly in terminal illness. mBC is an expensive disease to manage, requiring hospital-led care, medication, close monitoring, and often additional care givers. (Sorensen, 2012; Remak, 2004) This financial burden can negatively impact the lives of women with mBC and their families, and may result in them compromising some aspects of their care to reduce healthcare related costs. (Buzaglo, 2014) For more information on the economic burden of mBC, please see Section 2, Chapter 2: *Economic Burden of mBC*.

Healthcare professionals are directly affected by the impact of caring for a patient with mBC but do not receive adequate support

Healthcare professionals treating patients with mBC have reported a significant negative psychological impact on themselves. (Count Us, Know Us, Join Us, Psychological Impact, Novartis, 2014) Although not generally a primary focus, it has also been acknowledged that healthcare professionals involved in the care of patients with mBC may also be psychologically impacted. Oncologists make important assessments evaluating life expectancy of their patients with mBC on a daily basis and must discuss options with patients. (Filleron, 2015) Even experienced healthcare professionals may experience a degree of psychological stress when delivering difficult information to patients with mBC, including discussing

eventual death. In a US survey, 42% of oncologists said that treating patients with mBC had a significant negative emotional impact on them. (Count Us, Know Us, Join Us, Novartis, 2014) This may be due to limited treatment options. Similar to women diagnosed with mBC progression, a majority of healthcare professionals (67%) exhibited increased levels of distress when their patient's disease progressed, compared with an initial diagnosis. (Wardley, 2008) Healthcare professionals internalized the inadequacy of the first treatments they prescribed, had feelings of personal failure, and a notion that they had let the patient down. (Wardley, 2008) Clinicians also recognized that the disease state had now reached an incurable stage, with fewer treatment options available, which some patients might not fully realize. Physicians identified having developed closer relationships with their patients by this stage, increasing the difficulty in telling patients that their disease had recurred. (Wardley, 2008)

These surveys highlight the importance of adequate training and psychological support for healthcare professionals treating patients with mBC to ensure they can continue to care with compassion. It has been suggested that this could prevent possible questions in the minds of clinicians and patients about treatment adequacy and efficacy, which is important because treatment dilemma has been associated with a negative emotional effect.

Similarly to women diagnosed with mBC progression, a majority of healthcare professionals (67%) exhibited increased levels of distress when their patient's disease progressed, compared with at initial diagnosis.

(Wardley, 2008)



Chapter 4: Supportive Care Along the mBC Continuum

- There have been several areas of progress during the last decade in the supportive and palliative care of patients with mBC
 - mBC guidelines recognize the need for a holistic approach to supportive care that covers the entire disease continuum
 - Some cancer centers across the world have introduced and evaluated new approaches to delivering supportive care
- Access to wider and individualized support services is important to patients with mBC along their treatment continuum
- Access to effective supportive and palliative care is not yet globally achieved
 - Improved training is required for the broader multidisciplinary healthcare team to ensure palliative care is offered at the appropriate time
 - Patient- and family-focused information on supportive and palliative care is needed
 - Despite the impact of mBC on psychosocial health, access to mental health services is limited
 - Treatment adherence remains challenging and more support is needed

Breast cancer survivors have specific supportive care needs, especially those who are long-term survivors. Continuum of care for breast cancer starts with their first diagnosis of breast cancer. For women with eBC, it continues even after primary treatment for eBC. Patient education and support is needed to help survivors of eBC move from being cared for by their cancer care providers, to monitoring their own well-being. Survivors of eBC require education on recognizing disease recurrence or metastases, management of treatment-related events, psychosocial issues, and the importance of a healthy lifestyle. Their care will continue to require screening and ongoing support for symptoms or

consequences of their cancer treatment. (Ganz, 2013) Diagnosis of mBC is an important transition in the disease continuum, where the support needs change. Women who live with mBC have specific concerns that must be addressed throughout their lives, including health needs later on in life.

Recognizing that each patient's diagnosis and treatment path is unique, the following evaluation examines supportive care from a variety of perspectives. This includes evidence for supportive interventions, palliative care measures and survivorship support.



According to the EAPC, supportive care is suitable for patients still receiving anticancer treatment and for cancer survivors. (EAPC, 2009)

Terminology in this space is often confusing. The terms “supportive care” and “palliative care” are sometimes used interchangeably adding to the complexity. However, for the purposes of this report, supportive care in mBC is defined as the prevention and management of the effects associated with the disease itself or its treatment. This includes management of physical and psychological symptoms and therapy side-effects across the continuum of breast cancer—from primary diagnosis through initial neoadjuvant /adjuvant treatment, diagnosis of mBC and its treatment through to end-of-life care. Within this broad term, enhancing rehabilitation, survivorship, and end-of-life care are being considered integral parts of mBC supportive care and the overall patient experience.

According to the European Association for Palliative Care (EAPC), supportive care is suitable for patients still receiving anticancer treatment and for cancer survivors. (EAPC, 2009) Supportive care is especially important for patients with mBC, as a significant proportion of patients will remain actively managed for a prolonged period of time. However, there are significant gaps in supportive care for patients. Based on a survey of 568 respondents across 8 countries, 57% of patients with mBC receive palliative care but less than 5% have access to emotional and psychological support. (Breast Cancer Center Survey, Pfizer, 2015) Effective supportive care allows women to lead more fulfilling lives while living with their breast cancer.

In contrast, palliative care focuses on patients with very advanced mBC after active anticancer therapies have been withdrawn. (EAPC, 2009) It is an equally important part of living with metastatic disease, ultimately preparing for the end-of-life. The National Comprehensive Cancer

Network® (NCCN®) described palliative care as “a special kind of patient- and family-centered healthcare that focuses on effective management of pain and other distressing symptoms, while incorporating psychosocial and spiritual care according to patient/family needs, values, beliefs, and cultures”. (NCCN Guidelines® for Palliative Care v.1.2016) At some point along the mBC disease continuum, the aim of treatment will shift from the active treatment of disease to the palliation of symptoms, with the aim of minimizing distress and the impact on the individual’s ability to perform normal daily activities.

Methodology: In order to specifically address this topic a supplemental literature search was conducted for supportive care in patients with mBC. Please see Section 1: Appendix 1.4.

A There have been several areas of progress during the last decade in the supportive and palliative care of patients with mBC

There is a general consensus across guidelines that supportive and palliative care is needed for patients with mBC globally.

Evidence-based clinical guidelines for treatment of mBC, from international organizations (including those in both high- and low-income countries), recommend supportive and palliative care as part of mBC care. (Cleary, 2013) Some organizations with guidelines to note are the Breast Health Global Initiative (BHGI), Women’s Cancer Initiative, NCCN, and National Institute for Health and Care Excellence (NICE). (Cleary, 2013; NICE, 2014; El Saghir, 2015) All encourage expanding the concept of palliative care (previously limited to end-of-life care), to include supportive care offered concurrently with curative or life-prolonging treatments, for patients with all stages of breast cancer. (Cleary, 2013; NICE, 2014; NCCN Guidelines® for Palliative Care v.1.2016) In some places, access to palliative care may now be considered a human right.



A dedicated clinical nurse specialist with skills and knowledge of managing mBC would help alleviate the discrepancy between the level of supportive care received during treatment for eBC and after a diagnosis of secondary breast cancer.

(Secondary Breast Cancer Taskforce, 2008; Watts, 2011)

The BHGI and the World Health Organization (WHO) suggest introducing the concept of palliative care at the time of diagnosis of advanced disease or the initiation of treatment for advanced disease. (Cleary, 2013) These guidelines reflect the need to be able to identify and categorize common components of treatment-related supportive care for metastatic disease and end-of-life palliative care in order to establish evidence-based criteria for implementation of supportive care programs. (Cleary, 2013)

Some cancer centers across the world have introduced and evaluated new approaches to delivering supportive care.

Research on an electronic health questionnaire system, using algorithms based on patient reported outcomes, highlighted a high need for supportive care services for patients with mBC. Of the 983 patients included in the study, 623 (63.4%) received at least one referral to a supportive care service. (Wong, 2015) Opportunities for improved supportive services exist; in one study the introduction of a new mBC nurse role was found to improve the provision and organization of supportive care for patients with metastatic disease. The majority of patients were satisfied with the overall supportive care provided by the mBC nurse and perceived that the service had contributed to their care and well-being. Duties of an mBC nurse were

seen to be the provision of emotional support and information resources (ahead of coordination of care, clinical liaison, and provision of referrals). (Watts, 2011) A dedicated clinical nurse specialist with skills and knowledge of managing mBC would help alleviate the discrepancy between the level of supportive care received during treatment for eBC and after a diagnosis of secondary breast cancer. (Secondary Breast Cancer Taskforce, 2008; Watts, 2011)

In addition to specialist roles, specialist teams for specific care services could also provide benefit for patients with mBC. Palliative care focuses on a holistic approach to the management of distressing symptoms of disease incorporating psychosocial and spiritual aspects of care. (NCCN Guidelines® for Palliative Care v.1.2016) In a study analyzing the effects of specialist palliative care teams on outcomes for cancer patients, it was found that these specialist teams helped increase the amount of time spent at home by patients, satisfaction by both patients and their caregivers, symptom control, a reduction in the number of inpatient hospital days, a reduction in overall cost, and the patients' likelihood of dying where they wished. (Hearn, 1998) These teams required a specialist nurse, as well as the general practitioner, among other support staff, such as social workers, chaplains, therapists, etc.

Several cancer centers across the world have introduced patient-centric supportive care approaches. More details on these are in Chapter 6: *Approaches to Delivering mBC Care: Cancer Center Profiles*.

Countries and regions, such as Europe, have made advancements in palliative care through greater integration into mainstream health services. (WPCA, 2014) According to policy in the EU, anyone in need of palliative care should be able to have access to it. (Van Beek, 2013) While policies and regulations differ by country, there is a universal understanding around the importance of palliative care in helping to maintain quality of life in patients with mBC, despite its varied implementation.



B Access to effective supportive and palliative care is not yet globally achieved

Implementation of supportive care has been variable and significant gaps remain. Often, this requires an interdisciplinary approach and a shared objective of creating health systems that both identify and provide supportive care resources. Unfortunately, this coordination of effort may not exist today in even resource-rich health systems. A study conducted in Canada in patients with advanced cancer, assessed the impact of discussing palliative care on quality of life (measured using the FACIT-Sp scale). Although no significant difference in quality of life was observed between those who were told about palliative care upon diagnosis and those who weren't, patients did experience an improvement in an alternative measure of quality of life (QUAL-E) and satisfaction with care. (Zimmermann, 2014)

Data guiding palliative interventions, specifically in mBC, are sparse. (Morrogh, 2010) However, guidance on palliative care is being more widely represented in the literature independent of disease state and broadly across cancers. (Cleary, 2013; Cardoso, 2013)

Advances in palliative care have not been successfully implemented in all countries. (Harding, 2011; Sepulveda, 2003; Jeremic, 2014) For example, some types of palliative care (eg, access to pain medications) still remain unavailable in some countries, such as in Africa. Additionally, a systematic appraisal of the status of palliative care in Sub-Saharan African countries found limited evidence on the problems and outcomes of patients. (Harding, 2005) Although palliative care is now advocated as a global human right, (Gwyther, 2009) the research evidence in Africa to date has focused

almost exclusively on advanced human immunodeficiency virus (HIV), and specifically on the availability of opioids to improve both cancer and acquired immunodeficiency syndrome (AIDS) pain relief. (Harding, 2010; Logie, 2005; Cherny, 2013)

C Training for healthcare professionals on all aspects of supportive and palliative care is lacking

The primary focus of education around supportive care for metastatic disease and palliative end-of-life care should be on training multidisciplinary and interdisciplinary health professional teams and improving coordination of care. Patients with mBC should have multiple care providers that actively coordinate care as a key component of supportive and palliative care programs. (Cleary, 2013; EAPC, 2009; Cardoso, 2013; NCCN Guidelines® for Palliative Care v.1.2016) Efforts have already been made in some countries, to create interdisciplinary teams and educate primary-care physicians, nurses, and other specialists, such as oncologists and surgeons, in palliative care. Training of nursing staff in palliative care is important; currently, nurses report a lack of skills training, as well as confidence and tools needed to provide adequate palliative care. (Cleary, 2013)

Patients with mBC should have multiple care providers that actively coordinate care as a key component of supportive and palliative care programs. (Cleary, 2013; EAPC, 2010; Cardoso, 2013; NCCN Guidelines® for Palliative Care v.1.2016)



“ Patients and families should prepare in advance for this and should have people who are acceptable to the patient and capable of the work decided upon and lined up. Hours sitting in the quiet beside a patient as they rest and watching to make certain they aren’t in too much pain or having trouble catching their breath, calling hospice for advice, altering and administering medications, helping them on and off the toilet, which often will cause the patient pain— this can be daunting to the person who did not realize what they were signing up for and thought they’d just have a bit of pleasant conversation as they whiled away the afternoon with a friend. ”

“CJ” (Dian) Corneliussen-James, Co-Founder, President, and Director of Advocacy, METAvivor Research & Support, 2015

Additionally, training should ensure healthcare professionals are cognizant of relevant clinical practice guidelines for supportive care. Guidelines exist to support specific treatment-related toxicities, such as pain, nausea, vomiting and anemia. Guidelines on other supportive care topics are also available, including depression, rehabilitation, nutrition and exercise. These guidelines have been reviewed and detailed further as part of the 5th BHGI Global Summit for Supportive Care. (Cardoso, 2013)

Consideration should be given to the supportive care resources required for the management of the adverse effects of chemotherapy, radiotherapy and the complications of surgery and endocrine therapy. When resources to manage side-effects are unavailable or limited, effective treatment with limited toxicities should be considered. The optimal treatment goal is to have a full range of treatment options available and supportive care interventions to manage treatment-related side-effects. Monitoring for treatment-related side effects is considered part of routine breast cancer treatment protocols, but it is also an important part of supportive care throughout mBC disease progression. (Cardoso, 2013)

Health professional education in this domain should include the universal principles of pain management. This should include safe and effective use of strong opioids for mBC pain relief, understanding the relative differences in analgesic effects of various drugs, close and accurate clinical monitoring of patients’ pain levels and well-being, and identifying pain-related emergencies (eg, bone fracture, spinal cord compression, infection, or bowel obstruction). (Cleary, 2013) Pain control remedies should follow the WHO ladder, administered according to clinical practice guidelines. Basic nonpharmacologic pain management interventions should also be available and include management of pain-related physical symptoms. Patients’ preference for alternative and complementary pain medication should also be considered. (Cleary, 2013)



D Patients have identified a need for a wider range of support services

As patients with mBC progress through their treatment, support needs change in both intensity and type. Emotional support and quality of life improvements were identified as the top 2 needs of patients with mBC, beyond basic medical needs (Figure 1.5), in a primary research study with breast cancer centers. (Breast Cancer Center Survey, Pfizer, 2015)

In Europe, more than 40% of patients with mBC identified regular support from healthcare professionals as an area needing improvement, and more than 50% identified continuity of care and counseling specifically. (Harding, 2013) Despite differing levels of available support for patients, those with mBC may also not be aware of some of the resources available to them, such as telephone hotline access to specialist nurses and trained volunteers or access to in-person/online support communities. (Mayer, Lessons Learned, 2010)

Figure 1.5

Prioritized mBC Patient Needs

Breast Cancer Center Survey, Pfizer, 2015

| Support 79% | Quality of Life 72% | mBC Management 32% | Financial Support /Cost / Insurance 31% |
|---|---------------------------------|---|---|
| Emotional / Psychosocial Support | Pain Control / Management | Survival: OS, PFS | Especially US, UK, Australia |
| Family Support | Quality of Life | Effective / more effective treatment | |
| Social Support | Nutrition / Diet / Weight | Alternative / new treatment options | |
| Availability of caregivers / physician | Symptom Control / Management | | |

BCC Quant July 21-Aug 26, 2015

Q14, Q42 Base = Total Respondents (n=568);
Sweden included (n=582)

Q14, Beyond the medical needs that are focused
only on addressing the cancer itself, what do
you think are the top 5 most important needs of
*mBC patient? (Top 5)

*Stage IV / Unresectable Advanced BC

Respondents were from US, UK Germany, Italy,
Portugal, Brazil, Mexico, Australia, and Sweden

Research has identified that there are also generational differences in support needs for women with mBC. In the UK, younger women with mBC were more likely to rate the overall support they received as lower than older women; those who received formal support services felt they were beneficial, but a significant number did not know how to find these. (Reed, J Pain Symptom, 2012)

The majority of patients with mBC fail to access mental health services. Despite the impact an mBC diagnosis can have on psychosocial health, only around one-third of patients with significant anxiety or depressive symptoms access mental health services. (Mosher, 2012) This suggests an additional area of high unmet need in patients with mBC (Aranda, 2005), and a requirement for greater vigilance from healthcare professionals in detecting any alteration in mood, at early stages, to ensure patients are referred to the appropriate support services. (Kissane, 2004) Developing easily accessible interventions, such as telephone and internet-based counseling, may also assist patients who may face obstacles in accessing mental health services. (Mosher, 2012)



Use of mindfulness-based stress reduction (MBSR), a form of psychosocial support, has been shown to enable women with mBC to feel less reactive to emotional distress, while also reducing anxiety. (Eyles, 2015) Offering psychosocial intervention programs to patients with mBC, through social workers, also has demonstrated an improvement in outcomes, such as distress and despair, despite disease progression. The majority of patients found psychosocial interventions helpful with a greater than 10% decrease in prevalence of fatigue in these patients (baseline to 3 months). (Abernethy, 2010) Additional research is needed in this area to design effective interventions, that ensure women with mBC are being adequately and continually supported from a psychosocial perspective.

Support for mBC patients outside of families generally comes from adjunctive programs specializing in psychotherapy or support groups. (Abernethy, 2010) The support provided by patient support organizations (PSOs) will be covered in Section 2 of the report, *Policy, Society and Community Impact*.

Treatment adherence is another area where patients need support.

Globally, nonadherence with treatment is an issue in the management of mBC. In the United States, approximately one third of women with mBC report engaging in nonadherent treatment behaviors. Most commonly, patients in the study reported nonadherence due to forgetfulness (41%) and intolerance of side effects (37%). Nonadherent behaviors were found to be significantly associated with a decrease in functional well-being. (daCosta DiBonaventura, 2014) Nonadherence could be improved by simpler and less toxic treatment regimens that are as effective in treating mBC as more intolerable treatments. (daCosta DiBonaventura, 2014)

In a study evaluating how mBC patients value the attributes of different treatment options and how this subsequently impacts adherence, effectiveness was valued as 3 times more important than side effects.

(daCosta DiBonaventura, 2014) In this survey, patients described being willing to accept substantial additional risks from side effects for gains in overall survival. However, the severity of treatment-related symptoms or accumulation of symptoms over time significantly predicted early discontinuation or switching of treatment. This highlights how physicians may better maintain patients on planned therapy if they attend to the overall symptom burden that patients experience over time. This also reinforces the need for healthcare professionals to focus on symptom development during a patient's treatment and work to prevent and reduce symptoms as early as possible to help improve adherence. (Walker, 2014)

In some African countries, due to lack of national funding and access to adequate healthcare, poor compliance with treatment regimens is a major problem. Patients may have to bear the burden of transportation costs as well as the cost of diagnosis, overall care, chemotherapy, antibiotics, blood product support, and food and accommodation during treatment. (Adde, 2013; Abuidris, 2013; Adesunkanmi, 2006) This is also often the case for women living in rural and remote locations within more developed nations. While reasons for nonadherence differ, this is unquestionably a large problem worldwide.

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(daCosta DiBonaventura, 2014)



E Patient- and family-focused information on supportive and palliative care is limited

Improved communication about patient care and treatment options assists in understanding supportive and palliative care services available to a patient and their caregiver(s). Focus in this area should be paid to late-disease risks, complications of advanced disease, and palliative care treatments and their side-effects. In addition, patients and their families should be provided with information on pain management, skin care, and psychosocial and spiritual aspects of end-of-life care. (Cleary, 2013)

Early education of patients with mBC can help improve facilitation of future access to supportive care when needed. During active treatment, patient education should include recognition and management of treatment-specific organ-based toxicities and other treatment effects, including possible early menopausal symptoms, infertility, body image concerns, and sexual health issues. Patients should be further informed of the potential psychosocial complications related to treatment, such as anxiety and depression, and potential disruptions to their usual social roles, including employment and motherhood. (Cardoso, 2013)



Chapter 5: End-of-Life Care

- Studies have started to explore patient wishes related to end-of-life care and address challenges with delivering effective care
- Greater facilitation of doctor-patient communication about palliative and end-of-life care in a sensitive manner is needed
 - Healthcare professional may be reluctant to have such conversations or find it challenging to balance sensitivity and reality in their communication
 - Patients report that they find it difficult to talk to their healthcare provider about end-of-life care
 - Education of both patients and relatives about supportive, palliative, and end-of-life care is needed
- New collaborative approaches are needed to improve end-of life care for mBC patients
 - A disconnect remains between institutional models of care and the desire of patients for end-of-life care at home
 - An increased focus on timely hospice/palliative care referral is a crucial factor in providing high quality, individualized, end-of life care
- Better psychosocial support for women with mBC is needed to ease the end-of-life care experience

Each patient's experience is unique, but almost all reach a time where mBC leads them to face end-of-life. Based on a review for this report, no holistic reporting on the management of end-of-life care in patients with mBC has been identified, even though end-of-life care is one of the most distressing periods for patients, families, and caregivers and contributes to

a large proportion of healthcare costs for these patients. A transformation is needed to ensure that patients and families' wishes are met and ethnic and cultural sensitivities are also addressed in a patient-centric system. Policy makers, physicians, and patients must work together to improve end-of-life care for patients with mBC.



“ If the physician has been honest with the patient about prognosis, there are fewer misinterpretations about hope and extent of life. Oncologists must be able to say that the disease normally ends in death, but death can come at different times. For some, death may come within the first few years, but others live well for 5, 10, and even 20 years after diagnosis, and a few even survive the disease permanently. Oncologists should stress that no one can truly predict when the end will come and what it will be, but the best course of action is to prepare for every possible outcome. ”

“CJ” (Dian) Corneliussen-James, Co-Founder, President, and Director of Advocacy, METAvivor Research & Support, 2015

A Greater facilitation of doctor-patient communication about palliative and end-of-life care in a sensitive manner is needed

When discussing mBC with patients, physicians must carefully balance the dialogue to ensure a fair balance of sensitivity and reality. This is not to say that realities of mBC should be ignored. Primary research carried out for this report found that physicians currently first raise end-of-life discussions after multiple changes to treatment. (Breast Cancer Center Survey, Pfizer, 2015) Conversations about end-of-life care should be initiated earlier in the mBC treatment pathway, communicated using language appropriate to the changing situation, and tailored to the patient’s needs. Having this critical discussion sooner rather than later will increase the amount of time available for effective planning, and for some, not having adequate time could inhibit death preparation activities. (Chunlestskul, 2008) In reality, research completed for this report showed that, currently, in 65% of cases end-of-life discussions are held too late - first arising after multiple changes in treatment have already occurred. (Breast Cancer Center Survey, Pfizer, 2015) Effective and planned communication surrounding preparation for end-of-life is especially important for enabling women with mBC to participate in the process in an active and supported way.

Research completed for this report identified that, currently, in 65% of cases end-of-life discussions are held too late - first arising after multiple changes in treatment have already occurred.

(Breast Cancer Center Survey, Pfizer, 2015)

Oncologists play a vital role in determining whether palliative care and hospice services will be involved at all, and at what point of disease progression this will likely be accessed. (Kierner, 2010) Although conversations about end-of-life are extremely difficult for all involved in healthcare, it is crucial for healthcare providers to clarify patient and family preferences about care, location of death, and other requests. (Irvin, 2011)



Although conversations about end-of-life are extremely difficult for all involved in healthcare, it is crucial for healthcare providers to clarify patient and family preferences about care, location of death, and other requests. (Irvin, 2011)

However, such conversations can be misinterpreted by patients to mean there is no hope left, and this is one of many reasons why oncologists may be reluctant to have such conversations in the first place, or may find them particularly difficult. (Behl, 2010; O'Connor, 2015)

The role of families in making decisions on behalf of the patient has gained prominence. (Hauke, 2011) Education of both patients and relatives about supportive, palliative and end-of-life care may also help to address reports that family members/relatives do not always accurately interpret, communicate, or act on patient preferences. Family perception of patient wishes may also differ from the physician's perception. (Cleary, 2013; Hauke, 2011)

Advanced directives, or legal documents that explain decisions to be made at the end-of-life, can assist in conveying patient preferences, thus helping patients, families, and healthcare providers communicate more

Cultural or family traditions regarding the sharing of end-of-life decisions should also be respected, as they may differ from those of healthcare professionals or others involved in care. (Cleary, 2013)

effectively about end-of-life choices, and to definitively document patient decisions. (Cleary, 2013; Ozanne, 2009) It is important for patients to have full autonomy and power to make these choices on their own, without interference from external parties or even family members. It may even fall on the hospital or medical care center to ensure patients have this ability. Cultural or family traditions regarding the sharing of end-of-life decisions should also be respected, as they may differ from those of healthcare professionals or others involved in care. (Cleary, 2013)

Patients often find difficulty in speaking to healthcare professionals about supportive, palliative, and end-of-life care, despite the fact that a majority of patients with mBC report making plans for end-of-life medical care with others. Patients are more likely to talk to family and friends about end-of-life decisions than to their providers, and very few providers report an awareness of patient-led advance directives. Patients express a desire to share treatment decision-making with their provider; however, it is difficult to gauge success in reality. (Ozanne, 2009)

Greater facilitation of doctor-patient communication about end-of-life care is needed in order to provide high-quality patient care for patients with mBC. (NCCN Guidelines(R) for Palliative Care v.1.2016)

“ Most of the time, there is a misunderstanding between the specialist and patient. The specialist does not want to think about end-of-life and metastatic diseases. He does not want the patient to be depressed, so nothing is relayed to the patient about the truth of her disease. ”

Breast Cancer Nurse, France (Interview), 2015



B Changes are needed to existing supportive and palliative care models in order to further ease the burden on patients with mBC

The location of end-of-life care is a primary concern for patients and their families, and many existing models of care in mBC are centered on institutional care settings. (Cleary, 2013) A 2013 systematic review in adults from 8 countries with advanced or severe malignant or nonmalignant disease found that most people expressed a preference to die at home. (Gomes, 2013) However, factors such as culture, disease, and socio-economic status influenced the ultimate preference stated for home versus institutional end-of-life care. (Murray, 2009) Accessibility of pain relief, availability of affordable care, and the amount of assistance in coping with the burden of care were influential factors in patient choice of location for end-of-life care. Patient preference for the place of death may change over time due to a variety of factors, indicating a need for flexibility in care models, including preference for home care. (Cleary, 2013; Gomes, 2013)

These considerations are important, not only in high-income countries with high levels of resources, but also in low-and middle-income countries. In one Nigerian study, only 46% of patients dying of terminal breast

A 2013 systematic review in adults from 8 countries with advanced or severe malignant or nonmalignant disease found that most people expressed a preference to die at home. (Gomes, 2013)

cancer did so under hospital care. (Gukas, 2005) Reasons for patients' preference of dying elsewhere had not been studied, but it is proposed that the cost of terminal care, religious, and traditional beliefs may play a role. (Gukas, 2005) Unfortunately, this can lead to patients leaving hospital care and losing their life at home or in native herbal homes (treatment centers operated by herbalists) without appropriate management of symptoms, which can lead to severe pain, with sepsis, depression, and feelings of isolation. (Gukas, 2005) Since over 50% of terminally ill breast cancer patients preferred to die outside of a hospital setting in this study, the authors highlight that access to ambulatory care services that can support effective symptom control is necessary during the end-of-life stage of disease. (Gukas, 2005)

“ Most people may not know what hospice care can and cannot do. Staying in a hospice facility can be very expensive for the family. Also, when under hospice care at home, the patient will have support in her home for at best 2 to 3 hours per week. When the patient can no longer be left alone, she will have to find friends and family to sit with her. ”

“CJ” (Dian) Corneliussen-James, Co-Founder, President, and Director of Advocacy, METAvivor Research & Support, 2015



Reasons for patients' preference of dying elsewhere has not been studied, but it is proposed that the cost of terminal care, religious, and traditional beliefs may play a role. (Gukas, 2005)

The World Health Organization (WHO) state that palliative care is an urgent humanitarian need for people with cancer worldwide and recognize that it is particularly needed where a high proportion of patients have advanced disease for whom there is little chance of cure. Effective public health strategies, comprised of community and home based care, are essential to provide effective end-of-life care for patients and their families in low-resource settings. (WHO, 2015) In some countries in Africa, the absence of palliative care and hospice facilities may impair the quality of life in people with cancer. Whereas in India, hospice and palliative care services have become more widespread over the last 25 years through the notable efforts of individuals. (Khosla, 2012) The services remain early in their development and continue to face challenges including insufficient capacity in facilities, not enough trained personnel to meet population demand over a wide geographical area, and burdensome legislation that makes access to strong opioids difficult. However, a change in the mindset of healthcare professionals and national decision makers has occurred during this time giving impetus to the greater provision of palliative care. (Khosla, 2012)

The decision to refer a patient to hospice can be difficult, and many patients who enroll are referred very late in the course of their cancer,

preventing them from receiving most of the benefits of hospice care and support. (Irvin, 2011; Casarett, 2007) A survey performed in Austria indicated that Austrian oncologists contacted palliative care services later during the course of the patient's cancer and hospice services even later, even though early initiation of palliative care is recommended for patients with incurable diseases. (Kierner, 2010) An unplanned hospitalization in patients with advanced cancer may signal the time for palliative care consultation or hospice referral. (Rocque, 2013) Timely hospice referral or referral to specialist palliative care team is a crucial factor in providing high quality end-of-life care for patients with mBC. (O'Connor, 2015)

Better psychosocial support for women with mBC is needed to ease the end-of-life care experience.

Some patients with mBC experience high levels of anxiety, leading to a more negative and isolated end-of-life experience. Anxiety about death is associated with an increased rate of psychological problems. (Iverach, 2014) Many patients with mBC experience major concerns including the fear of dying and care at the end-of-life. (Mayer, 2010)

Severity of physical suffering, past history of depression/psychiatric illness, and a lack of social support can all increase the likelihood of depressive symptoms that may impact patient decision making around supportive and palliative care. (Cleary, 2013) Those involved in providing end-of-life care need to be aware that depression can be a cumulative response to progression of metastatic cancer and proximity of death.

Clear and compassionate communication between healthcare professionals, patients and families is a critical aspect of psychosocial care in any supportive or palliative care setting. Psychosocial care focuses on addressing the effects of cancer and its treatment on the mental and emotional well-being of patients and their families. (Jacobsen, 2012)



Clear and compassionate communication between healthcare professionals, patients, and families is a critical aspect of psychosocial care in any supportive or palliative care setting.

(Jacobsen, 2012)

The spiritual well-being of cancer patients is now recognized as an important consideration of care, and as a result, has been incorporated into cancer care programs. (Cleary, 2013; NCI, 2015) Attention to spiritual well-being may be helpful for patients with mBC, including faith, a sense of meaning, inner peace, and spiritual counseling, found either within or outside of religious practice.

Experiences at the end-of-life are naturally unique to each patient. A descriptive study of 5 women in Canada was conducted that sought to depict the experiences of women with mBC as they prepared for end-of-life. The women observed used a variety of methods to help themselves through this process, such as the open expression of feelings and giving themselves time and permission to grieve. Some women also did extensive cognitive work to prepare themselves for death, and they were able to identify their concerns (such as how should they be living, how could they say goodbye to their family, etc.) and valued their time in a new way by realizing that death could happen any time. They began to change their priorities and live life in a new, fully conscious way. (Chunlestskul, 2008)

Another highlighted need from patients was for healthcare professionals to be able to effectively assess their own attitude to death (as well as their patient's death attitudes) in order to rectify any emotional avoidance, superstition, or fear. Nurses in particular were identified as being able to fill the need of being conscious of death preparation and help patients to confront and manage it. (Chunlestskul, 2008)

Consideration of the range of support services available for patients, their families, and caregivers is important when initiating end-of-life discussions. Many women sought death preparation programs at different times while living with metastatic disease. Multigenerational support for family members was also an area of great need for patients with mBC, as end-of-life preparation not only impacts children of such patients, but also the parents of patients as well. (Chunlestskul, 2008) Bereavement support should be provided by the end-of-life care team to families according to assessed need and may include spiritual support in the community. (Cleary, 2013; Hudson, 2012) Women might prepare their families for their death by talking, using professional support (eg, a counselor), writing (eg, journals), and through role delegation. Part of this process could involve arranging wills, clearing out personal effects, and arranging for final preparations.

Individual counseling can enhance the ability of women to share and express their feelings about death without negative effects. It can also serve to help to clarify family problems and strengthen family well-being, so patients feel their families will function after they have gone. Regular participation in support groups can enable women to communicate with their family in a less emotional way and enable their family to start to prepare for their death. Support groups also provide a network for other women going through the same experience. (Chunlestskul, 2008)

Nurses have been identified as being able to fill the need of being conscious of death preparation and help patients to confront and manage it. (Chunlestskul, 2008)

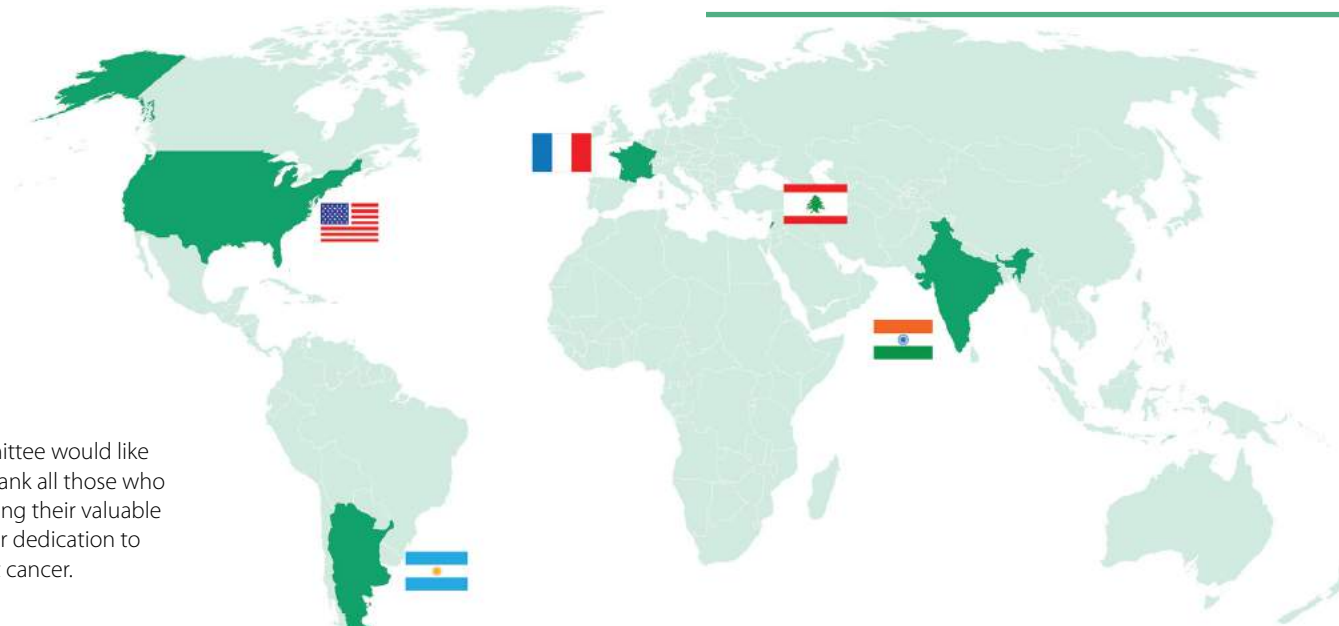


Chapter 6: Approaches to Delivering mBC Care: Cancer Center Profiles

The wealth of primary and secondary research reviewed in development of this report, provided an evidence-based approach to assessing the status of mBC. Perspectives from a vast range of stakeholders also highlighted how the findings translate into the everyday lives and experiences of patients with mBC, their healthcare professionals, families, and caregivers. Healthcare professionals play a pivotal role in treating and supporting patients throughout the continuum of their disease. Many cancer centers have developed and implemented their own approach to managing mBC patients that are tailored to local patient needs and socio-economic context.

While there are certain commonalities in approach, there are unique elements in each center's patient management and care delivery model, that provide valuable insights. Each is intended to provide a holistic and realistic view of the healthcare team's experience in caring for mBC patients, with the aim of sharing successes and challenges still to be overcome, in providing high quality cancer care.

Methodology: Interviews were conducted with 6 breast cancer centers from France, Argentina, Lebanon, India, and the US. Interviews were conducted with 2 to 3 positions working within each center to obtain a multidisciplinary view of how the centers address the needs of patients with mBC; these included: Directors, Oncologists, and Nurses.



The Steering Committee would like to recognize and thank all those who participated in sharing their valuable insights and for their dedication to patients with breast cancer.

USA:
MD Anderson Cancer Center
• Dr. Mariana Chavez-MacGregor
• Susan Ferguson
• Theresa Johnson

USA:
Queens Cancer Center
• Dr. Margaret Kemeny
• Linda Bulone

Argentina:
Instituto de Oncologica Angel H. Roffo
• Dr. Valeria Caceres
• Dr. Ana Cagnoni
• Esther Nunez

France:
Institut Curie
• Dr. Véronique Diéras
• Dr. Paul Cottu
• Sylvie Carrie

Lebanon:
Naef K. Basile Cancer Institute
• Dr. Nagi El Saghir
• Rebecca El-Asmar
• Mira Wehbe Hariri

India:
Tata Memorial Centre
• Dr. Sudeep Gupta
• Dr. Seema Gulia



1 The Nellie B. Connally Breast Center at MD Anderson Cancer Center, Houston, TX, USA

Participants: Dr. Mariana Chavez Mac Gregor, Assistant Professor, Department of Breast Medical Oncology; Susan Ferguson, Clinical Administrative Director; Theresa Johnson, Nurse Manager

Statistics:

Created as part of The University of Texas System, MD Anderson is one of the nation's original 3 comprehensive cancer centers designated by the National Cancer Act of 1971 and is one of 45 National Cancer Institute-designated comprehensive cancer centers today.

- Founded: 1941
- Patients per year: 40,000 of those approx. 80-100 new mBC patients

mBC Patient Population and Needs:

According to Ms. Ferguson, *"We see a whole spectrum of patients [at the Breast Center]. We see patients from around the world, as well as right in our neighborhood."*

In regards to the needs of mBC patients, Dr. Mariana Chavez Mac Gregor explained, *"The needs for each patient are different. mBC Patients are patients that have an incurable disease and are very likely to die. So throughout that journey, for some patients, support groups with patients that also have metastatic disease are very helpful. Support groups for those with early disease are much different than those with metastatic disease."* She went on to explain, *"Our [mBC] patients know what they have and they know we're not going to cure them. While difficult, this truth opens doors around discussing very clearly what we can accomplish with treatment and what we cannot."* Ms. Ferguson highlighted that mBC patients generally need a lot of psychosocial support. The center's members believe it is important to also provide support for the loved ones of mBC patients.

mBC Care Approaches:

Overall, a multi-disciplinary model is used for mBC patient care. Based on patient and disease characteristics, patients are triaged to the most appropriate department within the Breast Center. mBC patients may meet first with a medical oncologist, unlike eBC patients who might first be seen by the surgical team. As Ms. Ferguson explained, *"As far as what services for mBC patient care are provided to a new patient for their clinical care, we have algorithms and decision points. We have a very specific plan coordinated by physicians and staff for when a referral is needed for a new service."*

The multidisciplinary and holistic approach to care allows for the bundling of service appointments together which is especially beneficial for patients traveling great distance for care. All services collaborate together with the primary focus of the gain and good of patients.

Dr. Chavez Mac Gregor adds, *"We provide the best compassionate evidence-based care to our patients, especially when discussing clinical trial options and standard of care with our patients."*

"One of the greatest challenges is the discussion around palliative care and end-of-life; it's a difficult conversation for physicians to have and just as hard deciding when do you have it. Oftentimes, communication ends up happening in emergency department where patients are in pain and are now having an end-of-life discussion with a complete stranger."

Susan Ferguson



(continued)

The Nellie B. Connally Breast Center at MD Anderson Cancer Center, Houston, TX, USA

Challenges:

Ms. Ferguson explains, *“One of the greatest challenges is the discussion around palliative care and end-of-life; it’s a difficult conversation for physicians to have and just as hard deciding when do you have it. Oftentimes, communication ends up happening in emergency department where patients are in pain and are now having an end-of-life discussion with a complete stranger.”*

Despite ample resources, sometimes you cannot provide optimal treatment due to other challenges, such as patient financial constraints and physical conditions. In these cases, Dr. Chavez Mac Gregor explained, *“It’s not that we were doing something wrong. We do what needs to be done, but unfortunately it is very frustrating for everyone because the patient may not be in optimal condition.”*

Unique Features of Center:

All breast cancer nurses go through a robust nursing orientation program, which includes 4 to 6 weeks with a breast cancer center nurse mentor along with other educational aspects. As stated by Ms. Johnson, these programs *“make sure they have a foundation of breast cancer knowledge, including mBC, and signed-off before they can treat patients independently.”* All nurses at the Breast Center must be further certified in breast cancer care or oncology through a nurse educator program concluding in a certification exam. According to Johnson, *“The whole institution [at MD Anderson] has now implemented this as a best practice. What you see with certification in nurses is better patient outcomes.”*

Within the Breast Center, patients have access to nearly every service they may need. Outside of traditional oncology services, the Breast Center also has specific support professionals that are dedicated solely to breast cancer including, interpreters, social workers, pastoral services, pharmacists (PharmDs), and dieticians. Although separate from the Breast Center, MD Anderson also has several free services for mBC patients a dedicated Breast Imaging Center and a Breast Reconstruction Center.

Additionally, the Breast Center has its own beauty salon that provides several free aesthetic services. An internal store called “Appearances” is dedicated to personal items for women with breast cancer, including prosthetics, wigs, etc.

Ms. Johnson informed, *“The great thing about MD Anderson is that everyone that needs to be included to take care of your breast cancer is right here, within the same building.”*

Additionally, within MD Anderson, psychology professionals, international services (which provide support for international patients), a palliative care center, a pain center, and a survivorship center offer various services to all patients, including mBC.

“These programs make sure they have a foundation of breast cancer knowledge, including mBC, and signed-off before they can treat patients independently.”

Theresa Johnson





2 Queens Cancer Center (QCC), NYC, USA

Participants: Dr. Margaret Kemeny, MD, FACS Medical Director; Linda Bulone, Clinical Trial Manager Nurse

Statistics:

NYC has the largest public hospital system in the USA: the Health and Hospitals Corporation (HHC). QCC can be considered one of NYC's "safety net hospitals," which are hospitals that provide care to uninsured or low-income individuals.

- Founded: 2001

mBC Patient Population and Needs:

As the second largest borough in New York City, Queens has 2.3m people with 2 public hospitals taking care of all Queens patients without insurance or who are undocumented. Breast cancer is the most common cancer seen at QCC; approximately 20% of the patient population at QCC has this diagnosis. In addition, all patients have diverse needs due to cancer diagnosis and social backgrounds. Ms. Bulone notes, "In this community sometimes cancer is not the main problem the patient has... they don't have housing, jobs..." However, the director is keen to stress, "We treat patients regardless of their ability to pay." Due to the cultural and social backgrounds of the patients, many present with late-stage diseases such as mBC.

mBC Care Approaches:

QCC offers multi-modality cancer care. Patients are able to see surgical, medical, and radiation oncologists under one roof, and at the same time. Part of this interdisciplinary team is 3 social workers, one of which every new cancer patient sees, along with a nutritionist, pharmacists, and psychologist. The latter is particularly important for mBC patients as many have psychological distress as a result of their diagnosis. QCC also has its own geneticist, who may even test the families of mBC patients, while an anaesthesiologist runs a pain service within the Center.

"One of the unique features of our center is that we take time with our patients. We want to make the atmosphere as good as possible for the patients."

Linda Bulone and Dr. Margaret Kemeny

In addition to medical staff access, there are also a number of support groups for patients with general cancer and mBC, including monthly support groups run by psychologists, and often in collaboration with Patient Support Organizations (PSO). The external 'Gilda's Club' collaborates with QCC to run support groups for patients, which produce a variety of informative meetings such as nutrition and movement/dance therapy.





(continued)

Queens Cancer Center (QCC), NYC, USA

Palliative care is provided via an in-patient service only, and “Home Hospice” is engaged for patients at home; alternatively, patients enter a separate hospice facility. This may be facilitated by the pastoral or spiritual care service, another feature provided for patients by QCC. However, Dr. Kemeny emphasizes, “We really hand hold the patient through services, whether the services are on site or if they are offsite.”

QCC strongly supports access to clinical trials in a community hospital setting, providing opportunities to uninsured patients that they otherwise would not have elsewhere in the state. “It’s about getting patients access to new drugs that they didn’t have access to; everyone eligible for a trial will be screened,” says Dr. Kemeny.

Challenges:

Prior to the Cancer Center opening in 2001, a third of patients arrived at Queens with advanced or metastatic BC; this is a much higher number than the rest of the US. QCC works actively in the community to drive awareness of cancer and encourage patients to present earlier in their disease. As a result of a number of outreach programs, the number of advanced/metastatic BC patients at initial diagnosis at QCC has decreased to come in line with the rest of the country. Through the Queens public library system, QCC worked to promote mammograms by taking the “Mammo-van” to 20 branches for screenings. Ms. Bulone explains, “Education was very tailored to the communities, with community members telling us how they wanted to run the program.”

Some populations are more of a challenge due to cultural differences. “You know what you can do for them, and if they don’t let you do it, it becomes a very difficult

situation,” says Dr. Kemeny. QCC engages other tactics to help address cultural barriers; for example, enlisting local pastors, for instance, to join the consultation; however, patients ultimately make their own decision on how to proceed.

Unique Features of Center:

At QCC, 92% of patients fall into minority populations and 60% of patients are immigrants — as a result, QCC is truly multi-cultural and 105 languages are spoken by the population. QCC use a certified telephone translation service which facilitates conversation at visits.

In addition, QCC was successful in engaging an individual to act as a “Patient Navigator” through an external grant, thereby creating the Patient Navigator Program. In conjunction with the Center’s social workers, the Navigator meets with every new patient and connects them with outside resources such as meals, transportation solutions, cancer support groups, access to financial assistance during treatment, and outreach to other organizations. Both Dr. Kemeny and Ms. Bulone state, “We are not going to ever let the Navigator go, it’s too important for the patient.”

“One of the unique features of our center is that we take time with our patients. We want to make the atmosphere as good as possible for the patients. As a result this group of patients are very grateful – a ‘Book of Thoughts’ in the Center reflects this,” both Ms. Bulone and Dr. Kemeny explain.

“We really hand hold the patient through services, whether the services are on site or if they are offsite.”

Dr. Margaret Kemeny



3

Instituto de Oncología Angel H. Roffo, Buenos Aires, Argentina

Participants: Dr. Valeria Caceres, Chief of Oncology Department; Dr. Ana Cagnoni, Staff Oncologist; Esther Nunez, Nurse



Statistics:

The Instituto de Oncología Angel H. Roffo is a large teaching hospital associated with the University of Buenos Aires, specializing only in the treatment of cancers.

- Founded: 1922, the first oncology center in Latin America
- mBC Patients per year: 100
- Breast Cancer Appointments per year: 10,000



mBC Patient Population and Needs:

Of the entire breast cancer population treated at the hospital, approximately 20%-30% present at first diagnosis with metastatic disease, and a further 20%-30% are being treated for relapsed breast cancer. *"Many of our relapsed patients may have been initially treated elsewhere and are considered complex cases,"* explains Dr. Cagnoni. Often information about how patients have been previously treated is limited and this can make it more difficult to organize their ongoing care.

While holistic care for patients is available irrespective of the stage of breast cancer diagnosed, the participants noted that care of patients with mBC can be more complex than for those with earlier stage disease.

"Some patients may be seeing 10 or 15 doctors for different aspects of their mBC needs. We can deal with all of the adverse events and complications of disease that a patient with mBC could face."

Dr. Ana Cagnoni



mBC Care Approaches:

Organization of an individualized care plan is led by oncologists. Beyond providing and following up with their medical care, Dr. Cagnoni co-ordinates referrals for her mBC patients to other services and departments according to patients' personal needs.

Core to the success of this institute is the truly multidisciplinary approach to care with a team that includes a wide range of specialists, to support mBC patients holistically. This team consists of an oncologist, breast surgeon, palliative care clinician, radiation therapist, microbiologist or neurologist, and any other healthcare professionals needed. *"Some patients may be seeing 10 or 15 doctors for different aspects of their mBC needs. We can deal with all of the adverse events and complications of disease that a patient with mBC could face,"* said Dr. Cagnoni.

Psychosocial care needs can be complex, as the Instituto cares exclusively for patients who do not have health insurance. Patients may travel great distances and in some cases might not have the means to pay for transportation. Each patient is considered individually so that the most appropriate help can be offered. *"We have a social workers and psychologists that can offer 1:1 support for our mBC patients according to their assessed need. The service also aims to support families or caregivers where resource is available,"* said Dr. Cagnoni. Esther and the nursing colleagues play an important role in patient education, focusing patient education on approaches to maintain patient well-being during treatment as well as providing a point of contact and emotional support.



(continued)

Instituto de Oncología Angel H. Roffo, Buenos Aires, Argentina

Challenges:

Financial constraints prevent the center from increasing resources towards additional doctors to further meet the demands for services. Oncologists sometimes worry that they are unable to spend enough time with each patient. *“Patients with mBC need to be listened to. We need to give them time, space and attention and our first appointment can take 45 minutes or an hour,”* says Dr. Cagnoni. However, to provide additional support, volunteer doctors and “ladies in pink” come to help with patient care.

Building and infrastructure restrictions also have an impact on the services offered, but clinicians are well practiced at adapting. *“When there are no inpatient beds available, we offer very close follow-up to patients who need to be admitted. We would still like to be able to create greater access to clinical trials, currently this is very difficult in Argentina. We are also looking at service enhancements that ensure patient quality of life. This could be through exercise, meditation, or other support approaches,”* said Dr. Caceres.

A medical challenge includes changes in diagnosis. *“One of the most challenging parts of the breast cancer journey is the point at which care transitions over from active treatment to end-of-life care. There are few hospices in Argentina, as such, the palliative care team at the Instituto sets up end-of-life support at home with the help of the psychology department,”* said Dr. Caceres.

Unique Features of Center:

As well as referencing international best practice guidelines, the Instituto publishes updated cancer guidelines, that includes mBC every 2 years. The Instituto, through its links with the University of Buenos Aires, focuses heavily on the training and education of healthcare professionals. The Instituto runs an annual 3 day oncology congress which is attended by Argentinian doctors and provides a BC preceptorship program for doctors from other countries in Latin America. In addition, the Instituto has residency programs in clinical oncology and surgical oncology, which helps train healthcare professionals as part of this multidisciplinary team.

While the palliative care department is separate from the oncology team, its clinicians are integrated into treatment plan right from the start. *“All of our patients with an mBC diagnosis are offered an initial assessment appointment and about 80% will receive ongoing support. Help is focused on the management of any cancer symptoms that cannot be adequately treated in the clinic,”* Dr. Cagnoni explained. *“Within the palliative care center, we also offer non-traditional therapies such as acupuncture, massage and music therapy. Our specialist acupuncturist offers support to patients with pain that has been difficult to manage with more traditional therapeutic measures,”* said Dr. Caceres.

“Patients with mBC need to be listened to. We need to give them time, space and attention and our first appointment can take 45 minutes or an hour.”

Dr. Ana Cagnoni



4

Institut Curie, Paris, France

Participants: **Dr. Véronique Diéras**, Head of the Clinical Investigation Unit; **Dr. Paul Cottu**, Head of Service at the Day Hospital; **Sylvie Carrie**, Head Nurse, Medical Oncology Department



Statistics:

The Institut Curie exists in 2 locations: Paris/Orsay and the René-Huguenin Hospital in Saint-Cloud, all in the Paris region.

- Founded: 1921
- mBC Patients per year: 200-250 (new patients)



mBC Patient Population and Needs:

At the Institut, 50%-80% of the patients seen by oncologists have mBC, with 25-30 mBC patients seen per physician per week outside of clinical trials. One third of patients travel from up to an hour away, and a quarter come from a great distance, which is *"a big issue in the continuing care of these patients,"* according to Dr. Diéras. The Curie center was rated #1 for breast cancer treatment in France this year, so many patients are referred there for treatment.

According to Dr. Cottu, *"The biggest need of the mBC patient is to have some reassurance, some comforting words from the physician. Telling her that her life is not in danger in the short term, and she is going to be able to continue her normal life... they need to know that we will help them."*



mBC Care Approaches:

60% of a doctor's time during the week may be dedicated to the clinic. Breast nurses focus on organization of care and coordination with all the practitioners, which may include calls with the patient weekly to get updated information

"The biggest need of the mBC patient is to have some reassurance, some comforting words from the physician. Telling her that her life is not in danger in the short term, and she is going to be able to continue her normal life they need to know that we will help them."

Dr. Paul Cottu

and making referrals. The nurse keeps in contact with the patients' healthcare providers and any of the nursing teams that look after the patient at home, while coordinating with all teams in the Institut regarding patient care and treatment.



(continued)

Institut Curie, Paris, France

Challenges:

Caring for mBC outpatients in their hometowns is challenging. General practitioner care can be suboptimal, as the patients often may not get the systematic care they deserve, and it is difficult to take charge of that patient from a distance. A communication network is needed among all providers as there is a lack of information at the local level, and patients also need more supportive care service coordination including additional focus on care dedicated to the quality of life of the patient. There is no dedicated place for these support services in social systems, and *“women are sometimes alone,”* says Ms. Carrie. While government does provide some funding for these services, shortfalls exist that are through oncology networks funded by resources such as the mayor or administrative regions (government organizations).

Despite having all the tools required for effectively treating the patient in theory, in fact, resources cannot be applied to everyone. Some patients may not receive care due to personal choices or condition upon arrival. For example, Dr. Diéras feels that it would be advantageous for every patient to have a psychological review earlier in the treatment pathway: *“In mBC, at the beginning of their story if they could all see a psychologist to make sure everything is OK, and not wait for the 3rd or 4th line of therapy to be in the psychologists care.”*

Financial and space constraints are also evident in supportive care; more team members are needed, time spent with patients, education about the disease and treatment side effects, and translating what the specialist has told them, is not paid. Some people feel *“there is no value placed on taking care of the patient outside the prescription, no financial interest in taking care of the patient,”* Ms. Carrie commented. There is a need for someone in the hospital to link the patient between specialists, other doctors, the pharmacist, etc. *“to be there from the beginning to the end to help patients progress along their journey,”* continues Ms. Carrie.

A medical challenge in the treatment of mBC is the lack of accurate, specific prognostic data and predictive data that allow determination of the diagnosis and a choice of individualized therapy. *“Even if we won’t have a definitive answer for every patient, research will generate knowledge, and what we currently lack is knowledge. This is the next big step we have to go through in the coming years,”* says Dr. Cottu.

Unique Features of Center:

The role of the Nurse Specialist in mBC is being enhanced. Through a dedicated clinical nurse facility for mBC patients who have oral chemotherapy, 14 nurses on rotation specialize in caring for and educating patients on oral treatments and targeted therapy. The team undergoes continuous medical education regarding new oral therapies in cancer. Activities at the facility include patient counselling, and managing side effects and toxicities of treatment. Nurses can prescribe some basic treatments and refer back to the oncologist when required. There is a drop-in center staffed by 2 nurses that sees 10-20 mBC patients per day. Other hospitals have sent nurses to be educated at the center over last 2 years.

The Curie Institut also recently implemented a patient forum. mBC patients talk about their experiences, describe their disease course, what to expect from care, and details of their treatment to inform other patients. An outreach program is also in place to coordinate mBC patient care outside the institute.



5

Mamdouha El-Sayed Bobst Breast Unit, The Naef K. Basile Cancer Institute (NKBCI) at The American University of Beirut Medical Center, Beirut, Lebanon

Participants: **Nagi El Saghir**, MD, FACP, Professor of Clinical Medicine; **Rebecca El-Asmar**, Clinical Nurse Specialist (CNS), Breast Cancer; **Mira Wehbe Hariri**, Clinical Department Administrator



Statistics:

- Founded: 2007
- mBC Patients per week: 20 to 25, weekly or bi-weekly
- Patient Population: 50% under age of 50



mBC Patient Population and Needs:

Of the entire breast cancer population treated at the hospital, approximately 30%-40% present at first diagnosis with metastatic disease. They generally used to treat 60%-70% mBC patients, but this number has dropped considerably because of earlier diagnosis of BC due to awareness campaigns.



mBC Care Approaches:

The Breast Cancer Center is not a stand-alone, but rather a Center of Excellence within the Cancer Institute. This academic center offers service, teaching, and research, while caring for patients with all stages of breast cancer, and home care services are provided for many of their terminally ill mBC patients through non-government organization and palliative care teams. The multidisciplinary team includes radiologists, surgeons, pathologists, oncologists, nurses, residents, and interns, social workers and palliative care nurses. The center offers a full range of mammography and breast care services, using advanced technology. Patients can participate in global mBC clinical trials. Ms. Mira Hariri adds, *"In particular, a Data Management and Clinical Research Unit exists for researchers to collaborate and combine basic, translational, and clinical research to explore ways to prevent, control, and treat cancer, including mBC."*

At the institute, there has been movement into sub-specialization in clinical practice, research, and education programs for different disease sites. Dr. El Saghir focuses heavily on mBC patient education within his practice, as

well as highlighting its importance generally; *"The more the women know, the better their surgeon has to be. When they have more information they force the surgeon to do a proper treatment up front, because you know very often the upfront treatment is very important."* In affiliation with an NGO (The Lebanese Breast Cancer Foundation), The NKBCI Breast Center of Excellence runs breast cancer awareness campaigns, creates and distributes educational booklets, and organizes meetings in Beirut, other major cities, and in the countryside with local women's groups and charity organizations. Dr. El Saghir discusses breast cancer awareness, causes, detection, screening, and proper treatment. Dr. El Saghir focuses highly on mBC in particular. He states, *"We always make sure that when we talk about awareness we don't only talk early breast cancer, we make sure we talk about metastatic as well."*

"We like to involve the patients and be truthful with them; however, with advanced disease, is it important to tell the patients everything about it? Also, in this part of the world it is not easy to talk to patients very explicitly about their prognosis...For example, patients do not come alone to the clinic; there can be several relatives that fill up the room. The husband or sister may be behind the patients making signs to tell us 'please don't say everything to her', you learn how to manage between telling the truth and saying it step by step. You don't have to say everything on the occasion of the first clinic visit."

Dr. Nagi El Saghir

When choosing regimens, the patient is involved in the choice of treatment; but with advanced disease, the team tread carefully. *"We like to involve the patients and be truthful with them; however, with advanced disease, is it important to tell*



(continued)

Mamdouha El-Sayed Bobst Breast Unit, The Naef K. Basile Cancer Institute (NKBCI) at The American University of Beirut Medical Center, Beirut, Lebanon

the patients everything about it? Also, in this part of the world it is not easy to talk to patients very explicitly about their prognosis... For example, patients do not come alone to the clinic; there can be several relatives that fill up the room. The husband or sister may be behind the patients making signs to tell us 'please don't say everything to her', you learn how to manage between telling the truth and saying it step by step. You don't have to say everything on the occasion of the first clinic visit," says Dr. El Saghir.

As well as providing the best treatment possible, the center also focuses on the non-medical needs of mBC patients. Patient support groups are held weekly. They include survivors and family members, joined by breast cancer nurses and psychology nurses. The support group includes patients, regardless of their disease status, who not only attend the meeting but also participate in outside activities together. Ms. El-Asmar explains, *"The patients who have been through treatment give support to new patients, and are the most positive."*

Challenges:

Financial constraint creates the biggest challenge for care of patients with mBC in Lebanon. *"In this part of the world, lots of patients are uninsured and it's a big burden for them to pay for chemotherapy or drugs,"* says Dr. El Saghir. For many patients, their economic situation forces them to stop treatment, and they often prioritize the financial needs of their family over their health. Fundraisers are held to provide partial financial support for patients. Financial issues, palliative care and counselling in advanced breast cancer are major concerns the center tries to address. Ms. El-Asmar notes that the mBC patients and their families have the greatest need for these services.

Unique Features of Center:

The center employs a Clinical Nurse Specialist for BC, Rebecca El-Asmar, a very valuable resource to provide treatment continuity and patient support. Ms. El-Asmar states, *"Doctors may have tight schedules, so it is reassuring for the patients*

to have a Nurse Specialist who is there all the time... with recurrent patients, after 5 years some of these would ask for me, as we have a relationship, trust and a bond." Dr. El Saghir is a strong advocate for nurses in the breast cancer setting, *"It's really important to let the patients talk – very often they don't express themselves fully when they are in the doctor's office so we try to make sure the nurses take the time to do that. We need more specific breast cancer nurses in general, to spend more time with patients, and we need to pay better income for those nurses and support them personally, financially and psychologically as well. We also provide educational programs to help them advance their careers."*

An "emergency step-down" ambulatory unit to manage symptoms will allow patients to drop in without appointments, avoiding the emergency room where they have a long wait time and can be exposed to infections. Ms. El-Asmar notes that the mBC patients and their families have the greatest need for these services.

In addition, the center collaborates with other organizations around the world. Ms. Hariri adds, *"Internationally, we have established affiliations with sister institutions where we hold regular videoconferences and tumor boards for teaching, training, and management of cases. Regionally, we have established affiliations where meetings are held regularly to discuss research activities. Nationally, we are expanding our local medical services through affiliations with hospitals in different regions."*

"It's really important to let the patients talk – very often they don't express themselves fully when they are in the doctor's office so we try to make sure the nurses take the time to do that. We need more specific breast cancer nurses in general, to spend more time with patients, and we need to pay the income for those nurses and support them personally, financially, and psychologically. We also provide educational programs to help them advance their careers."

Dr. Nagi El Saghir





6 Tata Memorial Centre, Mumbai, India

Participants: Dr. Sudeep Gupta, Deputy Director; Dr. Seema Gulia, Medical Oncologist

Statistics:

This cancer center is a very high-volume hospital and is one of India's leading healthcare organizations.

- Founded: 1941
- mBC Patients per year: 4000 new patients, approx 400 have mBC

mBC Patient Population and Needs:

About 50% of mBC patients choose to receive their care near their home rather than at the center, usually due to geographic reasons or personal preference. Depending on their location and preferences, some patients may stay in proximity to the center while 40%-45% of patients return home after the initial phase of treatment. They will return for the response assessments, but most of the treatments will be conducted in local treatment centers, according to the original treatment plan provided by this center's team.

The participants noted that mBC patients require a greater level of supportive care compared to those with eBC. Additionally, there is a different level of counseling that is provided to these patients, as mBC patients require a more frequent assessment of disease progressions and have variable prognosis.

mBC Care Approaches:

Prior to coming into the breast cancer center, patients register online to streamline the process. Upon arrival, patients, including mBC patients, will be evaluated by a resident doctor within one to 2 hours. After this initial meeting, patients will also have the chance to speak with a faculty member and counselor, as well as have any additional tests and screening that may be required. With all of these steps, within 4-6 working days total, patients can have a full work-up completed to inform the care team, which includes all relevant healthcare professionals for the patient's condition, and focus on the extent of disease status and burden. During this time, patients will meet with a medical oncologist, surgical oncologist, radiation oncologist, and nurse who will help with treatment navigation. In these meetings, the care team will sit with the patient and

“We need to increase communications with other [cancer] centers.”

Dr. Sudeep Gupta

counsel them about the potential treatments, anticipated outcomes, and costs. According to Dr. Gulia, *“Starting at the point of registration at the center, patients can usually start chemotherapy within 7 to 10 days.”*

A big component to care within the center is a multidisciplinary approach. During the first week of a patient being registered at a center, a multidisciplinary team will meet in a “joint clinic” to discuss the patient. This group may consist of professionals such as surgeons, medical oncologists, radiation oncologists, radiologists, pathologists, nurses, or counselors. As mentioned by Dr. Gulia, *“These multidisciplinary teams are geographically located in the same location to ensure that patients can receive all of the care they require in one place.”*



(continued)

Tata Memorial Centre, Mumbai, India

Within the center, there are a multitude of services that are available for mBC patients such as medical oncology, counseling, genetic counseling, systemic therapy/radiation therapy, supportive care services, longitudinal care, and follow-up. Dr. Gupta noted, *"We provide high-quality pathology testing which is not a universal feature in a country like India."* A major difference to mBC treatment compared to eBC is in the provision of palliative care. The center has a full palliative care unit; with mBC patients, the center involves the palliative care team at the start of the treatment plan. By doing so, the center tries to "avoid abrupt situations," such as starting palliative care too late.

Because center is large academic cancer center, this provides opportunities for patients to be included in clinical trials for mBC.

Challenges:

Financial barriers are one of the biggest challenges for mBC patients at the cancer center and across India as a whole. *"Financial barriers may prevent patients from getting the best possible care in India,"* stated Dr. Gulia. She continued, *"A large fraction of the Indian population does not have access to formal health insurance,"* and therefore, they often need to provide their own financing for treatment. While the center is a public institution and will provide care to all patients regardless of the ability to pay, some therapies for mBC patients, like expensive targeted drugs, are not accessible to them due to lack of funding. While some NGO assistance is available, many of these therapies cannot be covered by these limited funders. The social work department will help link patients to philanthropic organizations and donors, but this is not always enough for mBC patients.

Additionally, there is an enormous shortage of medically trained personnel to care for mBC patients in India. As one physician stated, *"For every 50-60,000 patients in general, there is one trained medical oncologist. There is gross disproportion between persons who are trained for such patients versus the number of patients who need treatment."* Thus, services are stretched within the center and others.



"[mBC patients] need to know that they should be reporting as early as possible to the hospital to gain treatment. People are not aware and still think that cancer is a social taboo."

Dr. Sudeep Gupta

Lack of awareness and education among patients drives misconceptions and fear. As Dr. Gupta advised, *"They need to know that they should be reporting as early as possible to the hospital to gain treatment. People are not aware and still think that cancer is a social taboo."*

Unique Features of Center:

The center focuses on connectivity with other centers and institutions. Patients often come from far distances to receive treatment at the center and receiving follow-up care near their home can improve comfort and feasibility of care. In order to do this, the multidisciplinary care team develops a plan for treatment and communicates this plan with a local institution, even providing training if needed. Throughout the treatment process, the center stays in close contact with the local treatment team to follow-up regularly on patient progress. The center aims to send patients to remote institutions that they trust will provide good care to patients through following international guidelines.

There is a distinct understanding of the need for communication with local regions to better coordinate mBC care. As stated by Dr. Gupta, *"We need to increase communications with other [cancer] centers."* Many institutions do not currently have the capability to treat mBC patients adequately, but stronger development between cancer centers through training and increasing communication may improve care overall in India. This center is working towards this goal. *"Some basic care should be present at each center in India,"* as Dr. Gupta stated.



Emerging Recommendations

In review of the broad and complex needs and perspectives of patients with mBC, it remains clear that there are a number of unmet needs globally for patients, caregivers, and their families. Improvements in these areas will require the attention and action of a multistakeholder group, including mBC patients, healthcare professionals, policy makers, patient support and advocacy organizations and beyond, to truly drive change and better support patients living with mBC.

Education, Information, and Knowledge

A common theme identified within our analysis is centered on gaps in mBC-specific information and its communication between physicians and patients. Some key recommendations are outlined below:

- mBC specific training should be implemented for healthcare professionals and staff on how to better communicate with patients regarding mBC
 - National strategies are required to guarantee training needs are sustainably addressed
 - Communication skills should be an integral part of the oncology residency training and curriculum
 - Cultural sensitivity needs to be integrated into training
 - Provide psychological support for HCPs treating mBC patients
- Clinical trial information should be proactively discussed with patients in context of overall treatment
 - Discussion should address specific misperceptions
 - New communication and training approaches should be utilized



Jonny Salveron, mBC patient diagnosed in 2008, living with the disease

- Information and knowledge expansion for patients and caregivers regarding their disease and treatment options
 - Increased availability and comprehensiveness of guides to patients on diagnosis, treatment, and advanced planning
- Shared decision making between physicians and patients
 - Upfront discussions on multiple goals of managing mBC and patient priorities and preferences are needed
 - New approaches, such as decision aids, are needed to enhance patient participation and satisfaction in joint decision making
 - Treatment decision making should take into account the unique needs of older patients with mBC and avoid discrimination



Patient Care and Support Services

- Patients need multidisciplinary, holistic, and individualized approaches to mBC patient care
 - Improved understanding and training is needed for the broader multidisciplinary team to ensure individualized supportive care offered at the appropriate time in a patient's mBC continuum
 - Patient- and family-focused resources and services are needed that address physical and emotional aspects of care, especially for younger women
 - Greater focus on roles other than that of oncologist in providing holistic support – eg, the role of the specialist mBC nurse
 - Novel and patient-centric approaches to care implemented in several cancer centers around the world could provide valuable learnings and examples for other centers
- The role and impact of Patient Support Organizations (PSOs) is discussed in detail within Section 2
- Sensitive and realistic discussions about end-of-life matters should be initiated earlier in the mBC treatment pathway
 - Comprehensive psychosocial support involving patients, families, and caregivers is needed to ease the end-of-life experience
 - Communication training is key to ensuring all of these sensitive, yet critical, issues can be addressed with patients effectively by healthcare professionals
 - Patients, clinicians, and policymakers need to work together to improve end-of-life care for mBC patients

Quality of Life Research

- Greater focus and research into the factors that impact quality of life and effective psychosocial interventions to maximize this measure in mBC patients
 - There is a need for the development of validated clinical practice tools that can assess quality of life in real time at the patient level and help play a significant role in patient management in clinical practice
 - Research into psychosocial interventions should consider the emotional needs of caregivers and families



Section 2

Policy, Society and Community Impact



Introduction

In reviewing the status of the metastatic breast cancer (mBC) landscape, through a truly holistic lens, consideration of the societal factors impacting patient care is vital to understanding the complete picture.

Section 1: *Patient Care Perspectives* focused on discussing patient care and support needs along the care continuum, highlighting the extent to which they are currently being addressed globally and key emerging recommendations that could progress mBC patient care.

While direct clinical management and support for patients with mBC is crucial, it is not the sole aspect of how patients manage and live with their disease. The patient experience is also largely shaped by the surrounding environment, that both directly and indirectly affects patients with mBC. This section explores the breadth of political, societal and community factors that influence the mBC landscape.

As outlined in the introduction to this report, research into the policy, society and community impact has been designed to broadly assess the current status of mBC. Five core areas have been researched: Impact of mBC on Caregivers and Social Relationships, Workplace Perspectives, Policy Perspectives & Economic Burden, Societal Experience & Public Understanding, and the Impact of Patient Support and Advocacy Organizations in mBC.



Left to right: mBC patients Jen Sturtevant Meus, “CJ” (Dian) Corneliussen-James and Marlene King. Jen Sturtevant Meus, deceased. CJ was diagnosed in 2006. Both she and Marlene are living with the disease.

This section of the report shares key findings from primary research conducted in 2015 (methodologies are outlined in each chapter), it includes:

- **Health Policy of mBC**
- **Economic Burden of mBC**
- **Public Understanding of mBC**
- **The Impact of Patient Support and Advocacy Organizations (PSOs)**
- **Workplace Perspectives in mBC**
- **The Impact of mBC on Patient Social Relationships and Caregivers**

Research describing the complex relationship between support and coping with cancer is discussed in the *The Impact of mBC on Patient Social Relationships and Caregivers* chapter. Patient and caregiver experiences are



detailed, using their own voices, to determine key themes and ongoing unmet needs in this regard.

Work remains important and relevant to patients with mBC. In many countries around the world, but not universally, patients with cancer are protected from discrimination in the workplace and are entitled to ask for reasonable accommodations to be able to fulfill their job roles. Despite this, evidence of discrimination exists. Data discussing critical factors which support return to work are discussed in the *Workplace Perspectives for mBC Patients* chapter.

One of the most important factors affecting public understanding of mBC is the stigma associated with the disease. This is explored further within the *Public Understanding of mBC* chapter. In addition, as a key information source for the general population, traditional and online media are discussed and analyzed to provide an overview of their influence. It is of note, however, that an in-depth review of the impact of and information available via social media, and its impact, is required.

The role of PSOs in meeting support needs of mBC patients is also discussed in *The Impact of Patient Support and Advocacy Organizations* chapter, with a call for further secondary research to identify more ways in which these are and can be addressed by PSOs.



Chapter 1: Health Policy for mBC

- Health policy has a far reaching impact on mBC care; development is shaped by numerous factors and many different perspectives
- There are important differences in cancer care performance between countries which can be attributed to differences in the health policy approach
- A national cancer plan (NCP) sets out a country's ambition to face the demands of cancer
 - Many countries do not yet have a published NCP. In these countries, much needs to be done to incorporate cancer control as a national priority before a focus on improving the care of those with breast cancer can be implemented
- Published plans tend to focus on prevention and screening; this will not address the needs of patients already diagnosed with mBC
- Government, professional societies, and patient support organizations have all played a critical role in developing health policy that has started to contribute to the better care of breast cancer patients, including mBC, over the last decade
- Policy decision makers are going to need to find ways to meet the rising burden of cancer as a whole and breast cancer in particular

The influence of health policy on the outcomes and experiences of patients with breast cancer, including mBC, is far reaching; most notably on access to the care and treatment that patients need. Priorities set by governments are shaped by numerous influences and can change the way that breast cancer care is delivered; in fact, public policy touches every aspect of breast cancer.

“Health policy refers to decisions, plans, and actions that are undertaken to achieve specific healthcare goals within a society. An explicit health policy can achieve several things: it defines a vision for the future which in turn helps to establish targets and points of reference for the short and medium term.” (WHO, Health Policy, 2015)



Before discussing health policy specifically in the context of breast cancer, it is helpful to understand the breadth of factors that influence decision-making at a population health level and how this impacts wider cancer health policy. As shown in Figure 2.1, numerous inter-related elements influence and shape the political and health policy environment which makes the healthcare landscape complicated for patients, practitioners and decision makers around the world to navigate.

Figure 2.1

Factors Influencing Health Policy

Stevens, 1994

| Population Healthcare Need | Demand for Services | Supply of Healthcare Services |
|----------------------------|----------------------------------|-------------------------------|
| Determinants of health | Media and publicity | Historical pattern |
| Effective technologies | Available technologies | Public and political pressure |
| Evidence | Health professionals | Evidence |
| Financial support | Social and educational influence | Cancer registries |
| | | Resource limitations |

The relevant perspectives that inform health policy creation are diverse and include; patients, healthcare professionals, budget holders, national and international organizations such as professional groups, society itself, and the government. To optimize management of a specific disease area for any patient, the factors influencing, driving, and shaping health policy must be explored at both a global and an individual country level.

A Health policy has a critical role in improving cancer outcomes

It has been shown that successful health policy approaches lead to changes in the observed incidence, mortality and survival rates for individual cancers and, as a result, different policy approaches can be compared to identify those that create the greatest cancer health gains for any population of cancer patient. (OECD, 2013a) In an effort to answer the question “Do certain care policies lead to fewer deaths?”, the Secretary General of the Organization for Economic Co-operation and Development (OECD) reported the results of a study carried out in 35 countries to explore the policy trends in cancer care over a decade (2000 – 2009). (OECD, 2013a) The study found that there are important differences in cancer care performance between OECD countries which can be attributed to differences in the health policy approach in 3 main aspects of care:

- Access to resources including infrastructure, personnel and medicines
- Patient care practices including access to evidence-based care
- Governance including the development of national cancer plans

Of particular note, the report highlighted that breast cancer mortality declined across all OECD countries over the time period covered by the study. While the changes in outcomes are covered in detail in Section 3: *Scientific Landscape*, from a policy perspective, facilitation of early detection and access to treatments contributed to the observed decrease in breast cancer-related deaths. (OECD 2013a)



Methodology: Secondary research was undertaken; examining national cancer plans (NCPs) included on the European Partnership Action Against Cancer (EPAAC) website (<http://www.epaac.eu/national-cancer-plans>) and the World Health Organization (WHO) website (<http://www.who.int/cancer/nccp/en/>). While these sites are not comprehensive of all countries, this allowed for a high-level assessment of cancer plans around the world. Included in this review was an evaluation of the most recent (2014) NCPs for 25 countries in the European Union (EU) and 4 additional ex-EU countries (Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Slovenia, Spain, Sweden, United Kingdom, Colombia, India, South Korea, and South Australia (a southern state in Australia, as the health system is divided into regions)). All are accessible via <http://www.iccp-portal.org/cancer-plans>.

Increasingly, countries have set out their broad ambition to face the demands of cancer through a national cancer plan (NCP). The NCP is a public health program designed to reduce cancer incidence, morbidity, and mortality through “the systematic and equitable implementation of evidence-based strategies for: prevention, early detection, diagnosis, treatment, rehabilitation, palliation and research to search for innovative solutions and evaluate outcomes.” (EPAAC) The plan’s design aims to make the best use of available resources, promoting the most cost-effective measures that create the greatest benefit to the majority of the population. (EPAAC) The first plan was published in Germany in 1979 and, since then, NCPs have become increasingly prominent in many countries around the world. (OECD, 2013a) Even in high income countries, national targets captured within NCPs have traditionally focused more heavily on prevention and screening. However trends show that NCP targets are now maturing to include a broader focus on treatment, patient education and aftercare. (OECD, 2013a)

Across the 29 cancer plans reviewed in detail, the United Kingdom referred to mBC specifically. This NCP explicitly noted that a data gap existed regarding the proportion of breast cancer patients who had mBC. This in turn negatively impacted the national health systems ability to effectively plan for services. The cancer plan set out clear targets on a new approach to data collection in order to capture this information; with a stated aim to inform the collection of information on other types of metastatic cancer. (Department of Health, 2011) Despite this positive influence, outcomes for people diagnosed with breast cancer in the UK are lagging behind other countries in Europe. (Allemani, 2015; Macmillan, 2015) This suggests that in reality there can be a disparity between what is recommended in the NCP and what is implemented.

Across the 29 cancer plans reviewed in detail, the United Kingdom referred to mBC specifically.

The allocation of financial resource is also an important component considered in the development of national health policy. Decisions about achieving greatest benefit for the greatest number of the population can be quantified by methods including cost effectiveness analysis. A cost effectiveness comparison highlighted the impact of early vs. late mBC diagnosis in Africa/Asia vs. North America. The disability-adjusted life year (DALYs) recorded in this analysis included accounting for societal perspectives, and clearly underscores the economic drivers in the current climate of encouraging early detection and prompt treatment of breast cancer (Figure 2.2). (Groot, 2006) However, there will always be a population of patients who either progress to, or present with mBC, for which there is no cure currently identified. Irrespective of geography, this analysis also shows that the costs associated with treating mBC effectively are far greater than those incurred whilst managing early stages of breast cancer. (Groot, 2006)



The costs associated with treating mBC effectively are greater than those incurred whilst managing early stages of breast cancer. (Groot, 2006)

Figure 2.2

Cost Effectiveness Comparison of Treating Breast Cancer: Intervention Cost-Effectiveness by Breast Cancer Stage

Groot, 2006

| Disease Stage | Disability-adjusted life year (DALY) averted | |
|-------------------|--|---------------|
| | Africa/Asia | North America |
| Stage I,II or III | <\$390 | \$6,550 |
| Stage IV | >\$3500 | \$70,400 |

The incremental cost-effective ratios (ICERs) suggest that the priorities for national breast-cancer-control programs in these countries should be prevention or treatment of early stage breast cancer whenever possible. Results also indicate the high costs of treating mBC effectively.

B Over the last decade, global organizations and initiatives have been formed to shape breast cancer policy development and support national level implementation

In 2013 the World Health Organization (WHO) published its Global Action Plan for the prevention and control of non-communicable diseases (NCDs) which identified cancer control as one of the major priorities. (WHO, 2013) In some low- and middle-income countries, prominent public

health threats such as communicable diseases (eg, HIV, malaria) have caused the greatest pressure on governments. (Anderson, 2006) However, signatories to the global plan have committed to aim to achieve: (WHO, 2013)

- A 25% relative reduction in premature mortality from NCDs
- An 80% availability of affordable basic technologies and essential medicines

In a major step forward for mBC patients, the essential medicines list includes chemotherapy, hormonal, and HER2 targeted medicines that are considered core to the treatment of all 3 subtypes of mBC. (WHO, 2015b)

Moreover, the European Parliament, backed by EUROPA DONNA – The European Breast Cancer Coalition, adopted a written declaration “On the Fight Against Breast Cancer in the EU” in 2015. This statement followed previous Resolutions on Breast Cancer, (European Parliament, 2003; European Parliament, 2006) and committed that “those [with mBC] should have access to, and be treated in, a [specialist breast unit (SBU)], and their ongoing needs for care and psychosocial services should be coordinated and supported by the SBU.” (European Parliament, 2015) This builds on preliminary steps taken following the European Parliamentary declaration in 2010, which called for the European Commission to develop a framework for accreditation for SBUs by 2011. Debate amongst the medical profession about the need for specialist rather than generalist services for women with breast cancer, has been implicated in delays in implementation in some countries. (Knox, 2015) However, the 2015 declaration has reiterated the call to implement multidisciplinary SBU’s by 2016 and has been followed with a manifesto from the European Breast Cancer Council (EBCC) which demands action from the top - politicians and policy makers, and the bottom - grass roots patient advocacy and health care professionals, to drive through required changes to make this happen. (EBCC, 2015; European Parliament, 2015)



In a major step forward for mBC patients, the essential medicines list includes chemotherapy, hormonal, and HER2 targeted medicines that are considered core to the treatment of all 3 subtypes of mBC. (WHO, 2015b)

In recognition of the need to drive policy development in breast cancer around the world, organizations such as the Breast Health Global Initiative (BHGI), Union for International Cancer Control (UICC), Pan American Health Organization (PAHO), and WHO have developed knowledge summaries and 'calls-to-action' that make economically and structurally feasible recommendations for the care of patients with breast cancer. (UICC, Planning comprehensive breast cancer programs; UICC, Improving access to breast cancer care) By considering these resource-stratified, structured recommendations, countries can plan for cancer care as a whole and, ultimately, improve their provision of care for those with breast cancer including for those with mBC.

These guidelines stress the need for identifying needs and barriers, setting goals for outcomes and quantifying resources. Critical success factors include following a resource-stratified pathway that addresses:

- Structural barriers
- Sociocultural barriers
- Personal barriers
- Financial barriers

Such recommendations are helpful where the quality of cancer care as a whole requires improvement. In the majority of cases, however, recommendations focus on strategies to increase early detection of breast cancer. This is critically important but will not necessarily address the healthcare needs of patients who have already been diagnosed with mBC.

Over the last decade, many organizations have worked proactively to create progress in a number of key areas that influence health policy and which will result in better outcomes for patients with cancer, including breast cancer. Organizations include professional clinical bodies, non-governmental organizations and patient support organizations and some of the numerous examples of their work are described here.

// Organizations working in breast health can, and should, learn from one another. It's important that we share promising practices, exchange information and insight, and promote knowledge sharing about systematic, evidence-based approaches to improve the lives of women living with MBC. Komen engages with 1000s of national and international partner organizations and alliances to leverage resources to make the biggest impact. //

Kimberly Sabelko, PhD, Managing Director, Strategic Partnerships and Programs, Susan G. Komen, 2015



International professional societies such as the American Society of Clinical Oncology (ASCO), St Gallen breast cancer scientific committee and the European Society of Oncology (ESO) in collaboration with the European Society of Medical Oncology (ESMO) have spent considerable effort in influencing policy related to screening, diagnosis and treatment of breast cancer through publication of guidelines. These guidelines support a call to action for healthcare professionals to provide specific and tailored care to patients with mBC, as discussed in detail in Section 3: *Scientific Landscape*. (Coates, 2015; Partridge, 2014; Giordano, 2014; Ramakrishna, 2014; Van Poznak, 2011; Cardoso, 2014) This is important because such recommendations standardize approaches to treatment and promote the delivery of evidence-based cancer care. (OECD, 2013a)

In 2013, the European Society of Breast Cancer Specialists (EUSOMA) produced an update to their position paper, first published in 2000, (EUSOMA, 2000) identifying the minimum requirements to set up a specialist breast center. The 2000 iteration of the guidelines was widely acknowledged as best practice and informed the European Parliament Resolutions in Breast Cancer 2003 and 2006. (European Parliament, 2003; Wilson, 2013) In the 2013 update, which took into account recent advances in breast cancer diagnosis and treatment, EUSOMA recognized that the application of minimum standards and quality indicators would drive improvements in breast cancer care. As such, the position paper requires that specialist breast units must be able to provide continuity of care to patients with mBC through an integrated multidisciplinary team that includes access to a high quality palliative care service. (Wilson, 2013)

Furthermore, initiatives such as European School of Oncology (ESO) Breast Centers Network, and the Europe Against Cancer European Breast Cancer Network are a step forward in ensuring quality care for breast cancer patients through collaboration. (Breast Centres Network, 2014; EBCN) The efforts of both Networks aim to strengthen the evidence-base for

EUSOMA recommends that specialist breast units must be able to provide continuity of care to patients with mBC through an integrated multidisciplinary team that includes access to a high quality palliative care service. (Wilson, 2013)

cancer care. This will improve outcomes for all including those with mBC, and support policy makers in the development of their national plans for breast cancer.

In the US, the National Cancer Policy Forum, established by the Institute of Medicine, has brought together representatives from the government, industry, academia and consumers to debate critical policy issues in cancer care and research. (IOM, 2015) The reports created from these debates provide straightforward advice to decision-makers and the public about all aspects of cancer including issues critically relevant to those with mBC. Examples include access to affordable cancer therapies, biomarkers for molecularly targeted therapies and implementing a national clinical trials system for the 21st century. (IOM, 2015)

Additionally, the ASCO Institute for Quality is leading the development of CancerInq which will aggregate and analyze real-world cancer data in order to allow practices to benchmark, provide personalized insights into optimal care and uncover patterns that identify improved response to treatments. (cancerinq.org) Additional funding provided by Komen will support the implementation of breast cancer clinical decision support, a specific breast cancer patient portal and the development of breast cancer specific guidelines and measures within CancerInq. This will improve the quality of patient care and drive advances in clinical research



through greater communication and collaboration between breast care specialists. (ASCO, CCF, 2015) While it isn't clear how much of Cancerling resources will be targeted towards mBC, efforts like these are likely to improve the clinical management of breast cancer across all stages.

Furthermore, Patient Support Organizations (PSOs) have provided opportunities for patients to influence health policy themselves. Organizations such as Breast Cancer Network Australia (BCNA), Europa Donna, and Komen have contributed significantly in capturing the experiences of mBC patients and bringing them to the attention of policymakers. Further detail on the role of PSOs in shaping policy can be found in Chapter 4: *The Impact of Patient Support and Advocacy Organizations in mBC*.

C Country level implementation of BC policies has been variable and faces several challenges

Despite the availability of global policies for cancer generally, and breast cancer specifically, adoption has been variable around the world. Based on data collected by WHO in 2013, approximately 40% (79/194) of all countries do not have, or did not report, the existence of an NCP. In Africa, the proportion is higher, with almost three-quarters (39/54) of countries on the continent without a well-defined plan to address cancer. (WHO, Policies, strategies and action plans) In these countries, much needs to be done to incorporate cancer control as a national priority, before a focus on improving the care of those with breast cancer can be

Based on data collected by WHO in 2013, approximately 40% (79/194) of all countries do not have, or did not report, the existence of an NCP. (WHO, Policies, strategies and action plans)

implemented. Where cancer control planning is already more advanced, the focus for breast cancer continues to be limited to early detection and screening. (OECD, 2013a)

While the healthcare needs of a given population are a core contributor to shaping health policy, within or of itself, there are many layers to consider. There is significant variation in health policy for cancer-care between countries, (OECD, 2013a) with health priorities reflecting the most significant healthcare burden to the local population. Where funding is limited, interventions may be directed to areas where the most lives can be improved with the resources available. (Global Health Working Group, 2012)

There is significant variation in health policy for cancer-care between countries, with health priorities reflecting the most significant healthcare burden to the local population.

(OECD, 2013a; Global Health Working Group, 2012)

Variations in healthcare policy adoption may influence the differences observed between countries in important metrics such as breast cancer stage at diagnosis and mortality. As detailed in Section 3: *Scientific Landscape*, major differences in the rates of late diagnosis and breast cancer mortality leads to significantly decreased survival in lower income countries. (DeSantis, 2015; IARC, 2013; Unger-Saldana, 2014) Such disparities may be attributed to inequities in health service infrastructure and access to care, factors that could be impacted, at least partially, by national policies.

In low- and middle-income countries, variability observed in policy planning and implementation arise from access to both the financial and physical resources required to implement effective cancer care.



Here there is a link between the quality of cancer care and the state of healthcare delivery. Inherent limitations in the health system impede its ability to deliver improved outcomes for patients with mBC. (Anyanwu, 2011; Chalkidou, 2014; de Souza, 2015) Poor cancer outcomes have been linked to insufficient numbers of an appropriately trained healthcare workforce, limited access to screening and treatment facilities, inadequate supply of necessary drugs and timeliness of treatment after diagnosis. (Harford, 2011)

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Real-world Spotlight: Malaysia

A 2012 study from Malaysia described a low-cost program that combined healthcare worker training in cancer detection with measures to increase public awareness. The program improved identification of cancers of the cervix and breast, with a reduction in the diagnosis of advanced stages (III and IV) of both by approximately 50%. (Devi, 2007) Opportunities exist to raise public and primary care awareness and improve attitudes towards cancer diagnosis and treatment. (Erniah, 2012) It is clear that increasing breast cancer awareness in healthcare workers and the general population as a whole is imperative to address late diagnosis.

In realization of these issues, guidelines have been created that account for country-level differences. For example, the BHGI consensus statements provide guidance on resource allocation for supportive and palliative care for patients with breast cancer in low-income and middle-income countries. (Distelhorst, 2015; Anderson, 2006) Moreover, the clinical management recommendations included in the ABC guidelines were developed with consideration to their relevance to all countries around the world. (Cardoso, 2014) Despite these aims, implementation of some recommendations may still be impractical in low resource settings. (UCCI, Planning comprehensive breast cancer programs; Anderson, 2006)

Even among high income countries there are differences in outcomes for cancer including breast cancer. Factors such as socioeconomic status and access to healthcare services, contribute to disparities in cancer care in the US. (de Souza, 2015) Significant differences have been observed in the incidence rates, and mortality rates for breast cancer by race and ethnicity. (CDC, 2015) Therefore, it remains important for cancer initiatives to be designed to ensure equity of access to cancer care for minority populations. (de Souza, 2015) Moreover, in the UK, where outcomes for breast cancer lag behind that of other European countries, (Allemani, 2015; Macmillan, 2015) a new, independent cancer taskforce has identified 6 strategic priorities to improve cancer outcomes and transform patient experience. These priorities include a focus on improvements in public health, early diagnosis, patient experience, resource / infrastructure and commissioning. (NHS England, 2015) While these imperatives are a positive step, they continue to focus on early diagnosis and screening, and hence benefit patients with early-stage disease to the greatest extent; but targets to ensure better access to end-of-life care, clinical nurse specialists and improved technology will also begin to address the needs of mBC patients too.



“Each community, here in the US and across the globe, has unique needs when it comes to breast cancer. It is important to understand these needs, as well as the strengths and assets of the communities we serve, so that we can design evidence-based plans to reduce breast cancer mortality in each of these communities in the US and across the globe. To guide our programming, we work in partnership with local organizations and agencies to conduct health system assessments and community profiles that assess key breast cancer statistics, available infrastructure and quality of public health services, the factors that determine why women enter the breast cancer continuum of care, and the barriers that prevent women from completing the continuum.”

Kimberly Sabelko, PhD, Managing Director, Strategic Partnerships and Programs, Susan G. Komen, 2015

There is a lack of reliable data on mBC. Localized public health data is critical when decision makers are prioritizing healthcare expenditure. Although there are multiple data sources providing global and national breast cancer figures on prevalence of eBC, there are limited reliable global figures on prevalence of mBC. Some national data sets can be considered though, such as data from Australia estimating mBC prevalence to be 3 to 4 times the number of annual deaths from breast cancer. (Clements, 2012) As mentioned previously, policymakers in the United Kingdom recognised that the lack of data on the number of breast cancer patients with metastatic disease was impacting effective planning of services for these patients. Following an audit of the data available from existing sources, a recommendation was made to expand an existing mandatory data collection tool so that it specifically included information on patients with recurrent and metastatic BC. (NCIN, 2012) Low- and middle-income countries often do not have the capacity or tools to collect this type of data in a systematic way across disease states. (UICC,

Planning comprehensive breast cancer programs) Although there are exceptions which show that it is possible. In Kenya, for example, data for the single national cancer registry are collected from medical facilities in and around Nairobi. While this is a step in the right direction, information from the rest of the country is still absent. (Muthoni, 2010)

Despite clinical and technological advancements such as electronic health records (EHRs), disease registries and surveillance systems, even policy makers in high-income countries still lack reliable data regarding the burden of mBC. The data sets that are available suggest that the population of patients with mBC is continuing to grow. (Ferlay, 2010; Ferlay, 2015) However, without access to accurate numbers, policy makers cannot make informed policy decisions that will address the burden of disease in their communities. As such, policy makers may not sufficiently recognize the needs of many sub-populations, including those with mBC, which in turn creates challenges to the prioritization of resources.



The rising cancer burden increases pressure on constrained national health budgets. A detailed discussion of the economic aspects of mBC is included separately in Chapter 2: *Economic Burden of mBC*. However, in the context of health policy, the available health budget can influence policy development and adoption. (OECD, 2013b) Each country has its own priorities when financing healthcare and, as such, budgets vary considerably between nations.

The global burden of cancer continues to increase largely because of the growing and aging world population, alongside an increased uptake of cancer-causing behaviors, particularly smoking, in economically developing countries. (Jemal, 2011) Across the world, there has been a rapid growth in the direct costs of cancer treatment combined with an increasing constraint of healthcare budgets. (Kudrin, 2012) These factors combined show that the growth in healthcare spend has been driven by increasing prevalence of disease and growing costs of technologies and treatments.

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Budget holders are increasingly scrutinizing the cost of new therapies. Approaches which focus on a measurement of the cost effectiveness of treatments and interventions have gained greater prominence, even in countries such as France and Japan where Health Technology Appraisal (HTA) has historically focused on clinical efficacy. (Lim, 2014; Massetti, 2015; Kobayashi; 2012; Kudrin, 2012) The acceptable threshold at which new medicines are considered as cost effective differs between countries. (Kudrin, 2012)

Not all countries have established HTA processes. Those without an official, national HTA body may, or may not, complete some review based on cost before a drug is allowed to be used in the country. In this case, reimbursement is dependent on individual budget holders within that country. (Kudrin, 2012) However, this approach can lack transparency. Leading cancer centers and academic institutions in the US have urged for an evaluation and rating process similar to EU and other HTA countries to be applied prior to insurance coverage decisions and price negotiations. (Tefferi, 2015)

As a result of the different approaches employed around the world, the decision to fund any treatment can differ by country or region. One such example is Africa where there is variability in the national reimbursement of cancer treatments across the continent. In South Africa, best-practice cancer treatment is available at little cost to breast cancer patients within the public health system. (Dickens, 2014) In contrast, in Nigeria, patients personally bear the cost of cancer treatment, a formidable task for the majority. (Adisa, 2011) In one study, financial difficulties resulted in nonadherence to chemotherapy schedules in 45% of patients in the sub-Saharan region and also attributed to the infrequent use of new biological agents and subsequent lines of chemotherapy. (Adisa, 2011)



In one study, financial difficulties resulted in nonadherence to chemotherapy schedules in 45% of patients in the sub-Saharan region and also attributed to the infrequent use of new biological agents and subsequent lines of chemotherapy. (Adisa, 2011)

In conclusion, it is increasingly important for policy decision makers to find ways to meet the rising burden of cancer as a whole and mBC in particular. The resources required to meet this need are many and include, healthcare infrastructure such as access to hospitals, access to appropriately trained staff, radiotherapy, supportive care and cancer medicines. In breast cancer, while many of the treatments considered as standard-of-care are now available as generic products, (NIH, 2015) patients may still not have access to them as a result of other barriers in the health system.

Every opportunity to understand both the experience and needs of patients as well as the effective management of mBC through scientific research are invaluable. Such findings must be publicized and promoted

to national level health planners and policy makers to best inform health decision-making and could be applied in other countries around the world. Organizations such as the ABC Patient Advocacy Committee, Metavivor, UICC and Susan G Komen provide a forum to aggregate learnings to maximize steps-forward in mBC care. More in-depth research is needed to understand why current policy approaches haven't improved mBC survival and to identify the critical steps that need to be taken to create this step change.



"CJ" (Dian) Corneliussen-James was diagnosed in 2006. She is living with the disease.

// We question whether we've done everything possible to provide for and prepare our children, spouses and parents for the end that is coming - knowing it can happen suddenly. We push for equality... in support, in research...in survival; and many become activists. So much is going on with us...but what the public sees is our smiling face...just like every other smiling face out there. //

"CJ" (Dian) Corneliussen-James, Co-Founder, President, and Director of Advocacy, METAvivor Research & Support, 2015



Chapter 2: Economic Burden of mBC

- mBC has been associated with a significant economic burden to society and healthcare systems around the world
- Direct costs of mBC constitute mainly hospitalizations, emergency care, drugs and palliative care
- However, economic burden goes beyond direct costs of care and include lost productivity
 - For patients under 65 years of age, the indirect costs of mBC arising from lost wages for patients and caregivers and productivity losses for society through work absences and early retirement, can account for more than 50% of the total cost of care (Lidgren, 2007)
- Patients, families, and caregivers are bearing the increasing financial and humanistic burden of mBC
 - Indirect costs result in a decrease in household incomes for families and add to financial distress (Sorensen, 2012)
 - The impact of mBC on families and caregivers is often overlooked
- Broader understanding of the cost of BC is required to inform policy decision-making broadly (Lidgren, 2007)

Economic burden of mBC comprises direct and indirect costs.

The economic burden of cancer is significant, and continues to rise around the world. As our current review is focused on the economic burden of mBC, particular consideration must be drawn to the prevalence of this disease primarily in women, which exhibits additional unique societal challenges compared to other, less gender-defined, metastatic diseases. With women playing important roles both within and outside of the home, the impact of an mBC diagnosis is far-reaching. In addition, as women can often live for several years with mBC, they not only face the unpredictability of the ongoing and cumulative financial burden of living with the disease, but also the impact of the disease on their quality of life and ability to be productive members of society.

Methodology: In order to present a comprehensive overview of the economic burden of mBC from a patient, healthcare system and societal perspective, a literature review was conducted on the economic burden and cost of illness of mBC, reported over the last 10 years. See Appendix 2.2 for more details on literature search methodology. Within this report, the direct costs associated with treatment of metastatic disease are discussed at a population level, rather than at an individual level.

In considering the economic burden of any disease state, there are 2 main components 1) the direct costs of the treatment and management approach and 2) the indirect costs associated with the impact of the disease on the patient, caregivers and society. Figure 2.3 further defines what could be classified within each of the cost components and who bears these costs.



Figure 2.3

Classification of Direct and Indirect Cost Components

Sorensen, 2012; Lidgren, 2007; Broekx, 2011; Wan, 2013; Here & Now, Novartis, 2013

| | Direct Costs: | Indirect Costs |
|--------------------|--|---|
| Cost components | <p>Direct medical costs are those directly associated with disease treatment and resources used for medical care, eg,</p> <ul style="list-style-type: none"> • Hospitalizations • Surgery • Physician visits • Radiation therapy • Chemotherapy/immunotherapy • Oral drugs • Emergency care | <p>Indirect costs are the monetary losses associated with time lost due to disease or time spent receiving medical care</p> <ul style="list-style-type: none"> • Work departure (early retirement/temporary work absence) or time lost from other usual activities • Lost productivity due to premature death • Additional childcare needed while receiving medical care • Transport to and from medical care |
| Who bears the cost | <ul style="list-style-type: none"> • Health systems – governments, insurers, employers (insurance coverage for employees) • Patients and families (through individual/private insurance, and contributions such as copays) | <ul style="list-style-type: none"> • Patients, caregivers, families and more broadly, society |



While the literature review provided some published evidence describing the economic burden of mBC on individual patients and their families or caregivers, there were limitations in the depth and breadth of the data available. In addition, there were challenges in comparing data between sources, as summarized below:

- Most of the data regarding costs of mBC examines the direct costs relating to medical resource utilization at a healthcare system, rather than individual patient level. This is because most studies have been in countries where a national health system or system of health insurance pays for healthcare costs and not in countries where individuals bear these costs
- The majority of data available for patients with mBC is from higher income countries and is likely to underestimate the economic burden, since cancer registries are not always designed to provide complete information and disease progression is not always documented (Remak, 2004)
- There is a lack of data from middle-low income countries where extremely diverse socio-political and economic realities hinder prospective data collection and analysis, making extrapolation unreliable (World Breast Cancer Report, 2012)

- Comparative costs between high income countries have been difficult to make due to variations in healthcare systems and the definition of cost components examined
- Drug costs may vary depending on the year of analysis. For example, aromatase inhibitors which are the standard of care for HR+/HER2-mBC, the largest subtype comprising more than 60% of mBC, became generic in the US in 2010/2011. (Orange Book) Hence drug costs in this breast cancer subtype would likely be much lower after Loss of Exclusivity. Furthermore, trastuzumab, an innovative treatment for HER 2+ mBC, was approved in 1998 in the US, and significantly improved outcomes but also contributed to the increase in costs (CenterWatch; Eiermann, 2001)

A There is increased economic burden of mBC on healthcare systems and society

The direct cost of BC has increased and metastatic disease is a significant contributor to the costs. In Belgium, the average annual healthcare costs for women with breast cancer across all stages of disease, measured over a period of 6 years, was compared with those of the general population. Results from this study showed that the excess annual healthcare costs for patients with mBC were €23,280; greater than for patients with less advanced disease. (Broekx, 2011) (See Figure 2.4)

Figure 2.4

Excess Healthcare Costs per Breast Cancer Patient Over 6 Years According to Breast Cancer Stage from 1997-2004

Broekx, 2011

| Disease Stage (n=4,975) | Average Healthcare Costs per Breast Care Patient in the Sample (€) | Average healthcare costs of general population (€) | Difference (Discounted difference at 4%)* (€) |
|-------------------------|--|--|---|
| I | 19,827 | 10,610 | 9,217 (8,799) |
| II | 24,927 | 10,610 | 14,318 (13,461) |
| III | 32,606 | 10,610 | 21,996 (20,597) |
| IV (mBC) | 35,201 | 10,610 | 24,591 (23,280) |

*Given the 6 year time period, the net present value of costs in 1998 was calculated using an annual discounted rate of 4%



Cost comparisons between high-income countries have been difficult to make due to variations in patient cohorts and healthcare system funding. As an example, total direct costs which calculate the total medical and resource costs, measured by hospital use per patient, (both mBC and relapsed BC) range from €30,000 to €48,000 in Belgium, the Netherlands, France and the UK. (Frederix, Breast Cancer Research and Treatment, 2013; Bonastre, 2012; Thomas, 2009)

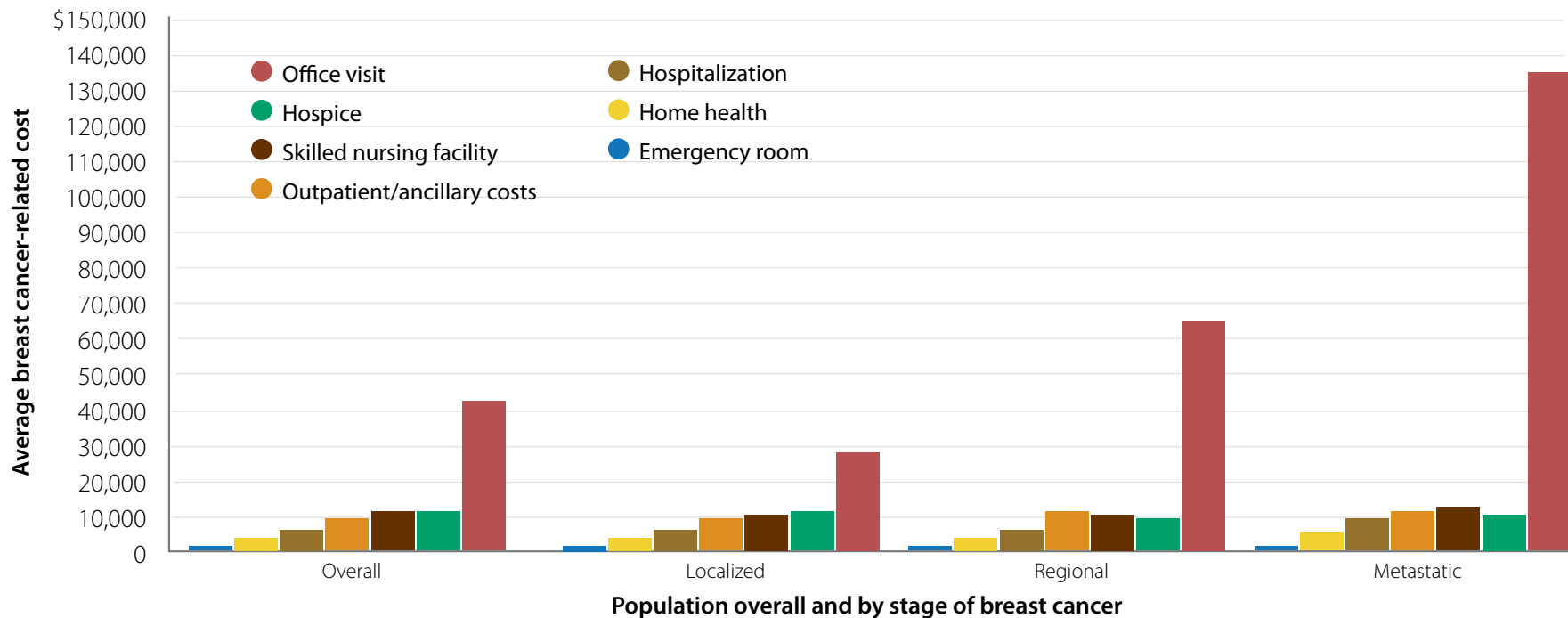
In the US, the cost per patient of mBC treatment to the healthcare economy is increasing. Medicare coverage is provided to people age 65 or older, people under the age of 65 with certain disabilities, and people

of all ages with End-Stage Renal Disease. (CMS, Medicare Program) Estimates in 1997-99, which included costs associated with inpatient hospital visits, skilled nursing facilities, physician/professional services, outpatient hospital clinics, diagnostic testing, home health, hospice care payments as well as payments for covered drugs, durable medical equipment, transport and supplies, show that the mean cost of treating a Medicare mBC patient in the US over an average of 16.2 months was \$35,164. (Rao, 2004) Using Bureau of Labor Statistics (BLS) published medical inflation data, this is equivalent to approximately \$52,700 in 2009. Davis et al analyzed the Medicare-SEER linked data to estimate costs, including

Figure 2.5

Average Adjusted Cost by Breast Cancer Stage and Category for Patients Diagnosed between 2000 and 2005

Davis, 2010



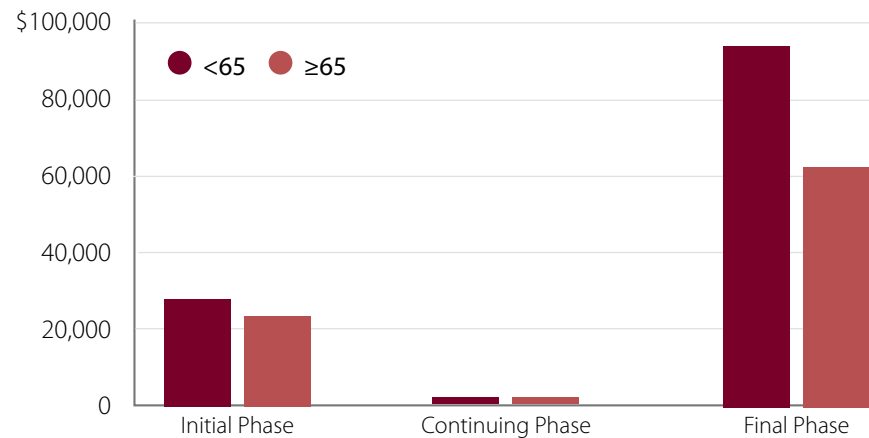
breast cancer-related surgery, radiotherapy, chemotherapy, and other medical encounters carrying a breast cancer diagnosis, and predictors of costs in elderly (≥ 65 years) patients diagnosed with breast cancer between Jan 2000 and Dec 2005 (see Figure 2.5). Cancer-related adjusted costs (2009 US \$) per mBC patient were reported to be \$153,421 over a median follow up period of 26 months (median time between diagnosis and death). Metastatic stage at diagnosis, amongst other factors, was found to be a significant ($p < 0.001$) predictor of higher costs. (Davis, 2010) Of note, based on an analysis including laboratory tests and diagnostics, surgeries and procedures, treatments, outpatient visits, hospitalizations including emergency department (ED) visits, and prescription fills factoring in the amount paid by the insurance plan, patient co-pays, deductibles, coinsurance amounts and out of pocket expenses, the cost of mBC per privately insured patient was on average, \$250,000 for an average life expectancy of 2.2 years in 2009. (Montero, 2012)

Cost of BC is the greatest in the final year of life. Mariotto et al (2011) published a projection of the costs of BC care in the United States, using SEER-Medicare linkage data, considered according to phase of care which they defined as initial (within the first 12 months from diagnosis), continuing (the period between initial and final phases) and final (last 12 months of life). This analysis of the direct medical cost estimates by phase of care, found that the average cost of treating breast cancer is greatest in the patient's final year of life (See Figure 2.6). Similar results were reported in a study from a Brazilian public healthcare system perspective. The analysis found that, even in the metastatic setting, progression of disease was associated with rising healthcare costs, with an increase from Brazilian Real (BRL) 308 in the pre-progression phase to BRL 731 post progression over one year. Furthermore, end-of-life costs were in excess of 5 times greater than in the post progression phase of mBC BRL 4,164 vs BRL 731 respectively (over the same time period). (Haas, 2013) These examples show how effective management at the end-of-life could have a substantial impact on the direct cost of cancer care in mBC patients.

Figure 2.6

Annualized Treatment Cost Trend for Managing BC in 2010 (USD)

Mariotto, 2011



Initial Phase = 12 months following diagnosis; continuing phase = the period between initial and final phase shown as cost per year; final phase = last 12 months of life

Indirect costs for mBC are significant to society. Indirect costs of mBC arise from lost wages for time off work (for the patient and their caregiver), unpaid caregiver time, and productivity losses for society. Ignoring these costs could lead to suboptimal policy decision making from a societal perspective and prevent women from comprehending the true financial burden of their disease. (Lidgren, 2007)

A large percentage of breast cancer patients leave employment due to their disease, and for breast cancer survivors, returning to work full-time can be a major challenge. (Meadows, 2010; de Boer, 2009) A 2015 retrospective US study demonstrated that breast cancer disease progression is associated with greater work hour loss in the work place. Results show that on average, non-mBC survivors miss 77-83 hours of work per quarter. In contrast, mBC patients during the end-of-life period, lose on average, 126 work hours per quarter (a 66% increase compared



to non-metastatic patients). The same study also confirmed that breast cancer progression contributed directly to an increased dropout rate from employment. (Yin, *J Clin Oncol*, 2015) A separate study found that mBC imposes a significant financial burden on patients through short-term disability costs (approximately \$6,000 USD in total) vs matched controls. (Wan, 2013)

Unfortunately the economic burden to caregivers is often overlooked and poorly understood. (Wan, 2013) More detail on insights gained into the experiences of caregivers in the work place is discussed in Section 2, Chapter 6: *The Impact of mBC on Patient Social Relationships and Caregivers*.

Sorensen estimated the annual US societal costs associated with treatment of mBC patients, using an incidence-based cost-of-illness (COI) model framework. An incident cohort of mBC patients was followed over 5 years, from diagnosis of metastatic disease, through active treatment (for eligible patients) and subsequently to end-of-life care and death. The incident cohort included both de novo patients and patients who had progressed to mBC from earlier stages of breast cancer and captured both direct and indirect costs. (Sorensen, 2012)

The model estimated additional economic burden of mBC in the US associated with loss of productivity of patients and caregivers to total nearly \$3 billion over a 5-year span, with the total discounted cost (ie, adjusted for inflation) to society being over \$12 billion (Figure 2.7). This represents a 3-fold increase in the cost of mBC to the healthcare system compared with data from the 1990s. The analysis included both direct and indirect cost estimates: utilization of cancer therapies and other medical care resources, treatment-related adverse events, diagnostic costs, lost income, and caregiver costs. (Sorensen, 2012)

Several studies suggest that the cost to society of mBC care is dependent on patient age, with the cost being higher for younger vs. older patients, specifically if indirect costs are also included. (Lidgren, 2007; Gordon, 2007; Broekx, 2011) One Swedish study demonstrated that for patients younger than 65

years of age, the annual total cost (ie, direct and indirect costs) associated with mBC was estimated as 334,000 SEK (\$46,500) vs 122,000 SEK (\$17,000) for those over 65 years. This large contrast in total costs was attributed to higher indirect costs for younger patients caused by absence from work and early retirement, accounting for more than 50 percent of the total cost. (Lidgren, 2007) The same study showed that mBC was associated with the highest rate of early retirement compared with the other disease states in women under 64 years of age. This results in a substantial decrease in work capacity in women advancing to metastatic disease. (Lidgren, 2007) Replacing the unpaid labor of European women in the grey economy would cost in excess of €880 billion. (Here and Now, Novartis, 2013)

Figure 2.7

The Estimated US Economic Burden of mBC*

Sorensen, 2012

| Group | Cost |
|--|--|
| Lost productivity of mBC patients and caregivers | \$2.9 billion indirect costs over 5 years = \$23,157 per patient-year = 23.5% of total direct and indirect mBC costs |
| Discounted cost (direct and indirect) to society of mBC (ie, adjusted for inflation) | \$12.2 billion accrued over 5 years = \$2.4 billion per year = \$98,571 per patient-year |

* An incidence based cost-of-illness model was developed in which an incident cohort of mBC patients are followed over 5 years, from diagnosis of metastatic disease and assessment of management course, through active treatment (for eligible patients) and subsequently to terminal care and death.



Annual total cost associated with mBC are higher in younger (<65) compared to older (>65) patients. The indirect costs of mBC can account for more than 50% of the total cost of care. (Lidgren, 2007)

B mBC imposes an increasing financial burden on families and caregivers

When evaluating the financial burden directly to the patient, their families and caregivers, there can be variation in how this impact is qualified and measured. As detailed previously in Figure 2.16, financial burden can constitute both direct costs, such as out-of-pocket payments related to the care that patients receive or cost of transportation to receive medical care, and indirect costs, such as the cost of childcare or home help needed to support family while receiving medical care.

Studies have highlighted a greater financial burden for patients with mBC than those with non-metastatic disease; this likely reflects increased disease severity, co-morbidities and side-effects associated with increasingly complex treatment strategies. (Zafar, 2013; Wan, 2013) Several surveys and publications describe the financial need and related concerns of mBC on the individual from an Australian, European and US perspective. For example, in a primary research survey, with breast cancer center healthcare professionals, 31% of respondents identified financial support as a top 5 unmet need for patients with mBC. (Breast Cancer Center Survey, Pfizer, 2015)

In an Australian survey of 579 women and 3 men with mBC, one-fifth of respondents identified financial assistance as an unmet need. (BCNA Survey, 2015) 49% of respondents were treated in the private health system and 44% treated in the public health system (7% of individuals asked did not respond). The survey found that 60% of respondents reported acute financial difficulty. For women in the public system, loss of income (37%) and out-of-pocket expenses (28%) were most frequently reported as the reason for these financial difficulties. (BCNA Survey, 2015) Women in the Australian survey were asked to provide estimates of their mBC related out-of-pocket costs incurred in the previous month. The values given ranged from \$0 - \$25,000 for women treated in the private health setting and \$0 - \$10,500 for women treated in the public health system; with an average total monthly out-of-pocket cost of \$687.17 for all women. Figure 2.8 demonstrates the breakdown of cost drivers contributing towards these out-of-pocket expenses. (BCNA Survey, 2015)

“The cost of treatment meant I used all my life savings... this is tough and has resulted in uncertainty... Am I going to have enough money to see me out? How does all of this affect my standard of living and therefore my relationships with family and friends?”

BCNA Survey Respondent, 2015



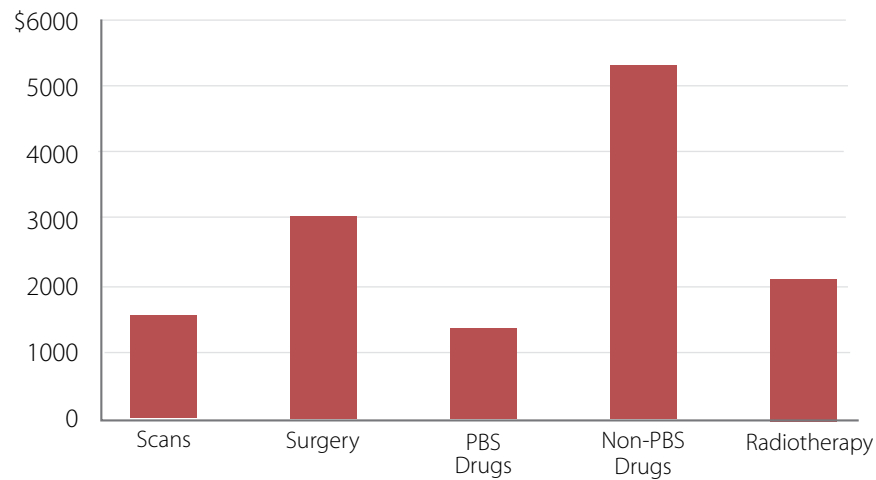
In an Australian survey, 60% of respondents reported they had experienced financial difficulty (within the previous week).

(BCNA Survey, 2015)

Figure 2.8

Aspects of Treatment that Have Incurred the Most Significant Total Out-of-Pocket Cost, Based on Data Collected from August-September 2014

BCNA Survey, 2015



PBS = Pharmaceutical Benefit Scheme

Based on an Australian survey of women with secondary (metastatic) BC (n=420)

Q: Which parts of your secondary breast cancer treatment have the most significant out-of-pocket costs, and how much has this cost you?

Respondents also identified other-out-of-pocket costs; including, travelling for treatment (eg, petrol, flights, accommodation and parking), associated treatment and care, such as second opinion appointments; complementary and alternative treatments, including vitamins, massage, naturopathy, Chinese medicine and practical assistance such as employing home help. (BCNA Survey, 2015)

“We are not on the poverty line, but I have lost half my wage and we relied on that to live.”

BCNA Survey Respondent, 2015

In the US, greater out-of-pocket expenses reflect a shift of some of the cost burden of cancer treatment from insurers to patients. Out-of-pocket expenses could include direct payments to providers, prescription drugs, as well as unpaid liabilities such as travel costs and lost wages. There is evidence that the related out-of-pocket expenses are particularly high for cancer care, (Zafar, 2013; Davidoff, 2013) and the associated financial hardship has negative consequences on care choices, quality of life, and disease outcomes. (Irwin, 2014)

Patients with mBC face greater financial burden and have higher per patient costs than for those with non-metastatic disease.

(Zafar, 2013; Wan, 2013; Davidoff, 2013)



European patients describe experiencing financial burdens arising from increased living costs and adverse changes in their financial situation. (Here and Now, Novartis, 2013) Additional living costs occur from travel expenses or check-ups, supplementary treatments, help around the house, or from special dietary needs. As a result, many women with mBC reported reducing expenditures on non-healthcare related items. Patients report that they are struggling to manage expenses (38% of women surveyed) including the mortgage (15% of women surveyed). In a European survey, the majority of women living with advanced breast cancer report a decline in household income as a direct result of their cancer, with 87% reporting an increase in living costs. The majority of women recognize a need for financial support. (Here & Now, Novartis, 2013)

Reductions in income can be significant, with one in 10 women describing a 50% fall in household earnings in one study across 11 European countries (Austria, Denmark, France, Germany, Greece, Italy, Netherlands, Poland, Spain, Sweden, UK). 62% of study respondents stated that they need improved financial support. Approximately 40% experience psychological and physical problems as a direct result of the change to financial circumstances. (Here & Now, Novartis, 2013)

In a US survey of 134 breast cancer patients, nearly one-third of which had mBC, financial distress was detrimental to patient well-being and response to medical care. Financial hardship included difficulty in paying for basic necessities (16%) and exhausting a patient's savings (19%). (Irwin, 2014)

Approximately 40% of women with mBC experience psychological and physical problems as a direct result of the change to financial circumstances. (Here & Now, Novartis, 2013)



“Travelling to hospital every day for treatment is incurring high petrol and parking expenses. Buying painkillers and other medication puts a big strain on our pension.”

BCNA Survey Respondent, 2015

A diagnosis of mBC brings with it a high degree of uncertainty about the future and the consequences of diagnosis on patient lifestyle, family, work and friends. In addition to the emotional and physical impact of diagnosis, there are financial considerations that patients must manage throughout the course of their disease. U.S. data shows the families of patients with mBC incurred nearly 40% higher indirect costs compared with those families of patients with eBC. (Wan, 2013)

Patient Concerns Following the Diagnosis of mBC

- What will be the financial impact of treatment?
- Who will continue to fulfill the role of homemaker, caregiver or breadwinner?
- How will the demands or consequences of treatment impact the way roles are managed and responsibilities completed?
- How will the loss of income and costs of care and treatment impact the family's financial resources?

Clear acknowledgement and communication of the economic burden of mBC and related financial concerns is required to inform policy decision-making and allow patients to have a clear picture of the potential financial burden to themselves and their families in order to adequately plan for the future. (Lidgren, 2007; Hunink, 2014)

Chapter 3: Public Understanding of mBC

- Public awareness and understanding of mBC is still limited even though public understanding of eBC has risen
- Global misperceptions about mBC prognosis exist, such as 'mBC is curable' or 'mBC has no hope'
- Patients with mBC may feel isolated and helpless due to a lack of understanding and stigma associated with the disease
 - Limited progress has been made to address these issues over the last decade
- Globally, variations in cultural bias impact public understanding and perceptions of mBC
- Perceptions and health-related behaviors around mBC can be altered through wider, more accurate communication of information on experiences with the disease
- Public exposure to messages regarding mBC has been increasing steadily over time
- Media communication has the potential to elevate the patient voice, reverse stigma and create a supportive environment for patients with the disease

Stigmatization of mBC increases women's health risks, isolates them from relevant resources, and prevents patients from accessing the medical and social support that are key to survival and maintaining quality of life. Often this can lead to women delaying presentation to a clinician until they are exhibiting symptoms of the disease. (LIVESTRONG report, Beckjord, 2012; Tfayli, 2010)

While public understanding of early breast cancer (eBC) has risen in recent years, it is generally thought that understanding of mBC specifically is inadequate. (MBC Alliance, 2014, Executive Summary) Although public understanding may not directly impact how a patient with mBC is treated, inaccurate perception from others in society matters greatly to a patient or caregiver. Inaccurate perception of disease implications, stigmatization,

and cultural attitudes, influence the social and emotional experience for all affected by an mBC diagnosis, whether they are patients, caregivers or families. There is much work to be done to improve societal understanding of mBC, with media likely to play a role given the positive effect seen in educating the general public on eBC.



Methodology: To better understand the general public's awareness, understanding, and perceptions of ABC/mBC globally, a general population survey was conducted during June 3 - July 30, 2015. In this survey, commissioned by Pfizer, a total of 14,315 adults aged 18+ from the general population (mBC patients and non-patients) participated. The 14 participating countries were: UK, France, Germany, Poland, Turkey, India, Taiwan, Japan, South Africa, Brazil, Mexico, Argentina, Chile and Colombia. In all countries, respondents were sampled from internet consumer research panels and invited to complete a 15-minute self-administered questionnaire in local languages; in Argentina, Chile, and Colombia; internet panel samples were combined with face-to-face interviews. In some countries (Poland, Turkey, India, Taiwan, South Africa, Brazil, Mexico), samples may not be fully representative of the population segment without online access, due to lower Internet penetration among the general public and/or less developed Internet panels in those countries. A similar (but not identical) survey was conducted in the US in 2014; n=2090 and formed the basis of the report: Breast Cancer: A Story Half Told, findings and recommendations, 2014.

Together, these studies represent the first, wide-reaching, global effort to assess public understanding and comprehension of both eBC and mBC. Results from these surveys provide a strong foundation for the findings within this chapter.

A Public awareness and understanding of mBC is lacking in the context of global breast cancer awareness

Global awareness of breast cancer amongst the general public is high. In a 2015 international survey of over 14,000 members of the general public across 14 countries, on average 54% of respondents knew someone with breast cancer. It is also the cancer with which adults are most familiar in the majority of countries surveyed across the globe. (mBC General Population Survey, Pfizer, 2015) These results echo findings of a similar survey conducted with 2,000 members of the general public in North America in 2014. (A Story Half Told, Pfizer, 2014)

National and international breast health awareness and promotional campaigns have been fundamental in increasing awareness of breast cancer over the decades. In turn, the building of support communities, an increase in the availability of information, and a movement for patients encouraged to take ownership of the detection, diagnosis, and treatment of their disease has been observed. Such activity has mainly been in the context of eBC and its survivorship, with limited focus on patients with recurrent, advanced or metastatic BC. (mBC Alliance, 2014) This is reflected in a global lack of familiarity with the terms 'advanced breast cancer' or 'metastatic breast cancer' compared with 'breast cancer' by the general population across a range of countries. (mBC General Population Survey, Pfizer, 2015; A Story Half Told, Pfizer, 2014)

“ For more than 160,000 women living in the U.S. with advanced, stage IV breast cancer, the situation is not one they can turn off on their TV sets, or avoid by skipping out from pink-decorated malls: they're living and coping with the metastatic form of the disease, active treatments, side effects and, still, no known cure. Their outlook is tempered, maybe best portrayed in a spectrum of gray. ”

Huffington Post, 2010



// We still have a long way to go and we are still losing too many women... but there is a lot more hope for many years of good quality life for a patient diagnosed with a metastatic recurrence now than there was 2 decades ago. //

Dr. Julie Gralow, fredhutch.org, 2014

In October 2009, the US Senate and House voted to support the designation of October 13 as a National MBC Awareness Day, as a result of the efforts of the Metastatic Breast Cancer Network. (Huffington Post, 2010; Metastatic Breast Cancer Awareness Day, 2012) Since 2010, this day has drawn attention to the unique needs and challenges of patients with mBC, across Europe and North America. (History of Metastatic Breast Cancer Awareness Day, 2013) While this is a positive step, the impact of this dedicated day has not been widespread and public knowledge remains limited, particularly regarding the distinction between early and mBC and the implications of these diagnoses.

The focus on early detection combined with significant advances in treatments for eBC, resulted in a perception that breast cancer has been largely “cured”. The “breast cancer survivor” identity obscures the reality that approximately 20%-30% of women diagnosed with eBC may eventually progress to metastatic disease, (O’Shaughnessy, 2015; EBCTGG, 2015) which is incurable.

Perceptions about mBC in society can be seen as 2 extremes: those who are optimistic about prognosis of the disease, and those who think of it as hopeless. In most countries surveyed, 47%-80% of respondents believed that early detection and/or treatment will prevent disease progression and 48%-76% believed that advanced breast cancer is curable, suggesting that there is a lack of public knowledge of the prognosis for patients with mBC (Figure 2.9). (mBC General Population Survey, Pfizer, 2015) The public perception of a breast cancer “cure” may impact patients’ ability, both newly diagnosed with mBC or recurring from eBC, to adjust perception away from “curing” their breast cancer to “living” with metastatic disease.

Despite those who hold expectations of finding a cure, globally, the terms ‘aBC/mBC’ and ‘breast cancer’ are associated with negative words by the general public. (mBC General Population Survey, Pfizer, 2015) There are also some perceptions of mBC as a hopeless disease and that the time and effort in treating mBC patients would be wasted, compared with eBC patients. (mBC General Population Survey, Pfizer, 2015) These extremities in perspective highlight a lack of awareness and understanding about the disease and how it differs from early-stage breast cancer.

// Breast cancer in this area [certain countries in Africa], is almost synonymous with stage IV, there are very little survivors. For these women a breast cancer diagnosis is a death sentence with little hope. //

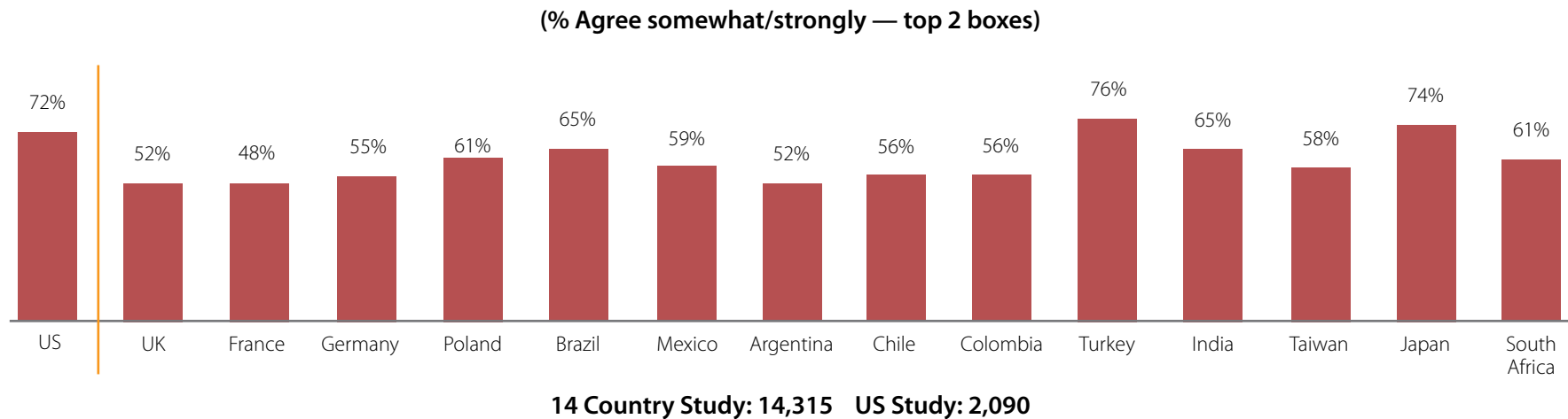
Dr. Olufunmilayo Olopade, Director of the Center for Clinical Cancer Genetics, University of Chicago, 2015



Figure 2.9

Percentage of the General Public Surveyed that Believe Advanced or Metastatic Breast Cancer Can Be Cured

mBC General Population Survey, Pfizer, 2015; A Story Half Told, 2014, Pfizer



For all countries except the US, the percentage of respondents who either somewhat agree or agree strongly with the following question: 'How much do you agree or disagree with the following statement about advanced or metastatic breast cancer? "Advanced or metastatic breast cancer is curable"' (mBC General Population Survey, Pfizer, 2015). This research was not powered to draw comparisons between countries.

*US respondents totaled 2090. Responses were obtained via a separate survey asking whether respondents strongly agreed/agreed that patients with breast cancer can be cured if caught early with the right treatment.

“ I think the minute you say metastatic or secondary [breast cancer], people just think they’re on their way out, why should we bother putting research money to it...and that makes it really difficult to research this group of patients separately. ”

European Respondent, mBC PSO Survey, Pfizer, 2015



B The lack of broader understanding of mBC negatively impacts mBC patients' experience while living with their disease and adds to stigma, distress, and isolation

Sadly, a significant proportion of the public believe that breast cancer

“People don’t understand the word metastatic to begin with...And when I’d tell them I was stage IV, they’d give me pity or stay away or see me a year later and think I was a ghost. They couldn’t believe I was alive.”

US mBC patient, fredhutch.org, 2014

progresses or recurs because patients do not take preventative measures, such as correctly taking medicine and attending appointments. (mBC General Population Survey, Pfizer, 2015) These findings were echoed in a similar survey of the public in the US. (A Story Half Told, Pfizer, 2014) Negative public perceptions of mBC impact the association that mBC patients have with the disease.

“Positive messages about lifestyle choices that might reduce breast cancer risk or those that focus on early detection may in a subtle way reinforce the misperception that these things will be effective for everyone – and that if someone develops breast cancer or metastatic breast cancer, it must have been their fault.”

*Kimberly Sabelko, PhD, Managing Director,
Strategic Partnerships and Programs, Susan G. Komen, 2015*

Nearly half of patients with mBC report feeling social rejection in the form of isolation, shame and feeling like outcasts, particularly within the breast cancer community. (MBC Alliance, 2014) These elements are characteristic of the mBC experience in the overall population as well, and influence patient behaviors such as their willingness to seek support or make treatment and quality of life decisions. It is notable that the feeling of isolation identified in mBC patient surveys from 2008-2009 are still present in later studies, highlighting the limited progress over time in changing perceptions of mBC. (Faces of mBC, 2010; MBC Alliance, 2014)



“But dealing with an incurable illness and the side effects of its treatment aren’t the only burden MBC patients have to bear. Many also have to educate others about their disease, explaining over and over that no, the scans and blood tests and treatments will never come to end. No, the metastasized breast cancer in their lungs is neither lung cancer nor linked to smoking. No, staying positive and ‘just fighting hard’ isn’t going to beat back their late-stage disease.”

fredhutch.org, 2014

Results from a 2013 global survey of 1,273 women with mBC in 12 countries demonstrated that, regardless of country income level, most women with mBC felt that others do not empathize with their experience. Nearly two-thirds (63%) of women said they “often feel like no one understands what they are going through” while two in five women said they “feel isolated from the non-advanced breast cancer community” (see Figure 2.10). (Count Us, Know Us, Join Us, Novartis, 2013) This sense of isolation from the larger breast cancer community can be attributed to a lack of available resources to address their needs, appropriate messaging and the negative perceptions associated with a terminal diagnosis. This isolation is mirrored, globally, by the general public where 18%-49% of people indicated that patients with mBC should keep it a secret and not discuss it with anyone other than their physician (Figure 2.11). This was most pronounced in India and Turkey, where almost half of people surveyed agreed with this statement (49% and 42%, respectively). (mBC General Population Survey, Pfizer, 2015)

Figure 2.10

Percentage of Women with mBC by Country Who Feel Their Experience is not Understood by Others and Feel Isolated from the Breast Cancer Community

Count Us, Know Us, Join Us, Novartis, 2013

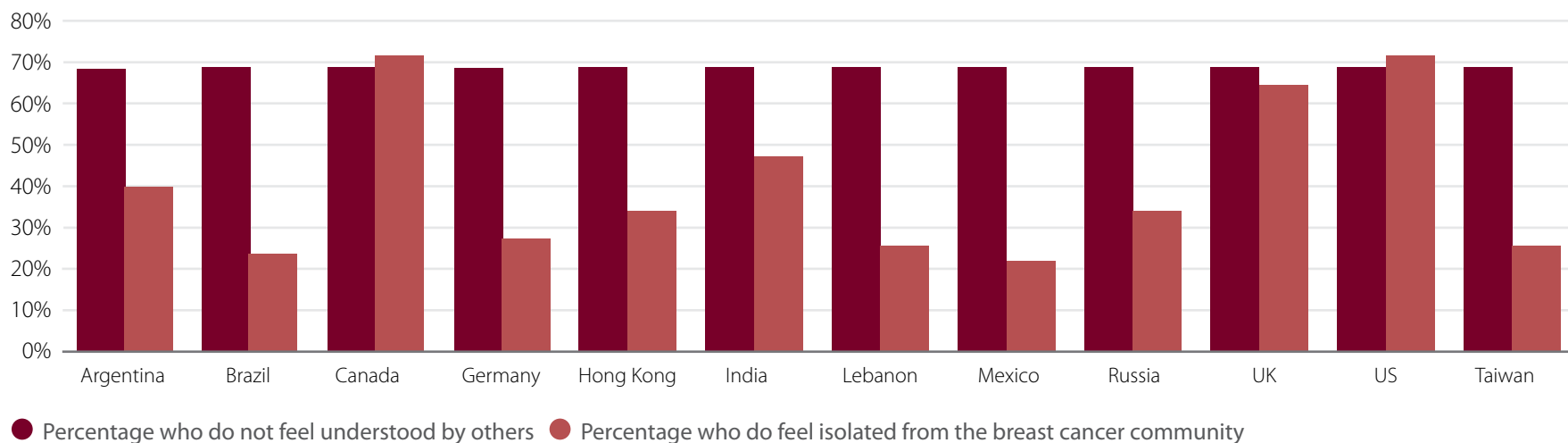
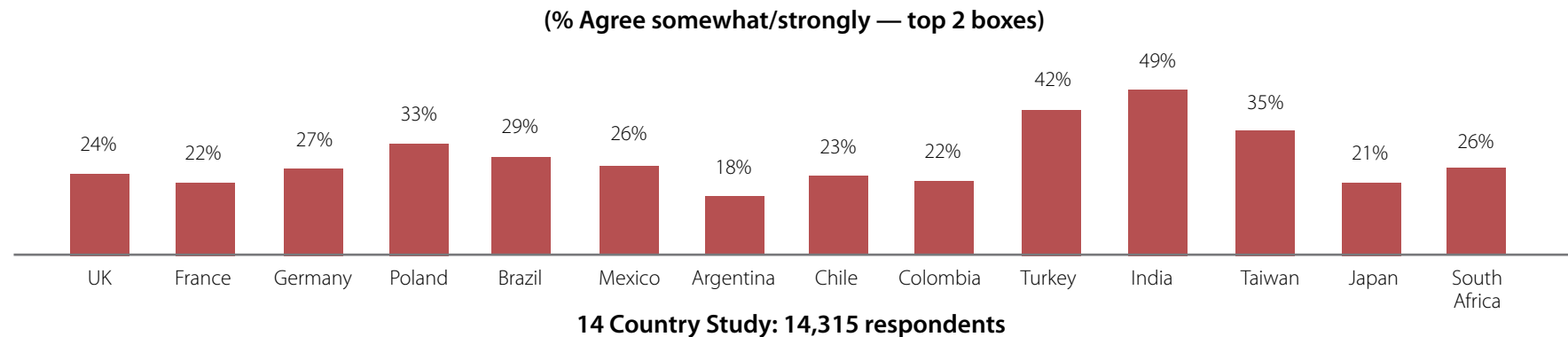


Figure 2.11

Percentage of General Public Respondents Who Felt People With Advanced or Metastatic Breast Cancer Should not Talk About It With Anyone Other Than Their Physician

mBC General Population Survey, Pfizer, 2015



On average, 28% of the general population indicated that patients with mBC should keep it a secret and not discuss it with anyone other than their physician.

(mBC General Population Survey, Pfizer, 2015)

While the majority of breast cancer patients are female, men also are diagnosed with both early and advanced disease; globally, an average of 69% of people are aware that breast cancer occurs in men as well as women. (mBC General Population Survey, Pfizer, 2015) Literature shows little information regarding men, and specific research is needed to understand how men's needs differ from those of women.

The overwhelming focus on eBC in messages conveyed by the media, breast cancer awareness campaigns and the association between early disease and survival, generates the perception of 2 distinct breast cancer patient groups: those who survive and those who die as a result of their disease. The treatable, yet incurable nature of mBC means patients with advanced disease do not fall distinctly into either of these groups. This "gray area" impacts patients with metastatic disease with respect to their quality of life and their level of distress along disease continuum. These patients are considered to be "without a voice" in the general breast cancer community. (Count Us, Know Us, Join Us, 2013; Inside Vandy: Vanderbilt University, 2013; Metastatic Breast Cancer Network, 2015; History of Metastatic Breast Cancer Awareness Day, 2013)



“The way we [in the US] talk about breast cancer has fundamentally changed over the past 4 decades. Prior to the 1970s, breast cancer was a taboo subject -- many did not dare to say the words “breast cancer” aloud. We’ve overcome that stigma, and now, across the globe, we need to do the same for mBC.”

*Kimberly Sabelko, PhD, Managing Director,
Strategic Partnerships and Programs, Susan G. Komen, 2015*

The journey to change perceptions of eBC has taken many years and the level of success differs geographically. In the 1970s the journalist Rose Kushner shared with the public, not only her experience but also the science behind her breast cancer. She successfully combined her own story with the basics of cell biology, using everyday language to reach

her audience. (Ryan, LA Times, 2014). Over the years, public figures willing to take a similar plunge and share their experiences have helped make conversations about breast cancer more acceptable. (Beckland, LA Times, 2014)

In some developing countries, there still remains a need to overcome a stigma associated with breast cancer, overall, before strategies to change the perception of mBC, specifically, can take effect. Local culture and beliefs that can discourage patients from seeking care early-on, include the physical implications of treatment (especially mastectomy), lack of access to knowledge about breast health, and family/community rejection following a breast cancer diagnosis. The lack of options for early detection due to limited access to routine care and examinations, as well as lack of access to affordable, high-quality treatment options contribute to the poor outcomes for patients with breast cancer and perpetuate the negative image of breast cancer in these communities. (Shulman, 2010)

“ Because it is such a devastating diagnosis, women (in some sub-Saharan African countries) feel that they cannot let anyone know that they have cancer, isolating them from help and support from friends and family. The stigma is so high that women stay under the radar. By the time they come out, the breast is fungating and smelling, leading to them being ostracized from society furthering hindering them from getting help at the time they need it the most.”

Dr. Olufunmilayo Olopade, Director of the Center for Clinical Cancer Genetics, University of Chicago, 2015



Enhanced media attention (traditional and online) towards mBC has the potential to shape public perceptions and create a supportive environment for mBC patients

The availability of accurate, relevant information on mBC is essential to create a uniform cultural understanding of the disease, that will in turn help stimulate a sense of community and provide a supportive environment for mBC patients. Currently, there is a lack of specific, robust public information from sources felt to be trusted. Globally, less than half of the general population feels that reliable information on advanced or metastatic BC is easy to access (Figure 2.12). (mBC General Population Survey, Pfizer, 2015) Perhaps reflective of this lack of available information, a US survey highlighted that 61% of the general population knew little to nothing about mBC. (A Story Half Told, Pfizer, 2014)

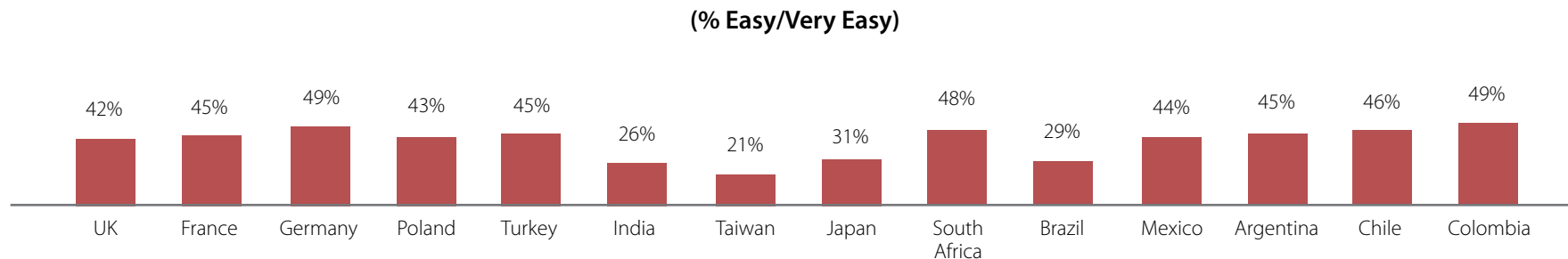
In a survey of 14 countries around the world, when considering specific information sources, those surveyed receive information on breast cancer through traditional media (TV, radio, newspapers etc.) as well as the internet; and approximately a third of participants rely on charitable organizations to provide relevant information. (mBC General Population Survey, Pfizer, 2015)

Given the reliance on media as a source of mBC information, a deeper analysis of media coverage on mBC was conducted. The analysis began with assessment of 2 core articles reporting on the role of media (BRIDGE Metastatic Breast Cancer Patient Survey, 2010; Fishman, 2010) The BRIDGE survey results revealed that over 50% of patients felt that BC received too little public attention; 73% of those surveyed wanted increased public awareness of mBC, including a greater level of media attention for people living with the disease (60%) and more recognition of public figures with the disease (55%). (BRIDGE Metastatic Breast Cancer Patient Survey, 2010)

Figure 2.12

Access to Reliable Information on aBC/mBC

mBC General Population Survey, Pfizer, 2015



A 2010 analysis of cancer news reports from 8 large-readership newspapers and 5 national magazines from the US highlight the limited focus on mBC; only 13.1% of 436 articles reported that aggressive cancer treatments can fail to cure or extend life, or that certain cancers are incurable (Fishman, 2010). Reports on cancer treatments and outcomes have included information on aggressive treatment options and patient survival, with seemingly little focus or discussion on the prognosis and treatment outcomes for late-stage cancers or terminal diagnoses, such as mBC. (Fishman, 2010) This may have portrayed a view of treatment for advanced disease that is inappropriately optimistic, leading to an unrealistic perception of the mBC patient experience. Furthermore, articles infrequently discussed treatment side effects, such as neuropathy, pain, hair loss and nausea, which are common to cancer treatments. (Fishman, 2010)

Since these findings were reported in 2010, some progress has been made in increasing public exposure to mBC. To compliment these surveys, an analysis of yearly distribution of collected newspaper articles and newswires between 2006 and 2014 was conducted (see Appendix 2.3).

Methodology: In order to gain an understanding of public exposure to information on mBC, a qualitative literature review was conducted using secondary source data restricted between the years of 2005 to 2015 from LexisNexis®. Key word searches were conducted in LexisNexis® and were restricted to the years of 2005-2015 resulting in 998 abstracts. A standard TF-IDF text mining method was used to assign weight to the word stems

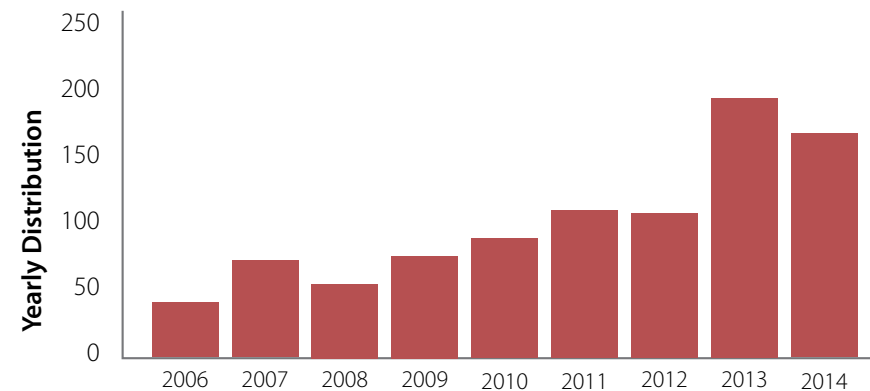
identified in each article. Initial text mining analyses rendered 13,824 word stems covering a broad range of subject areas. For the year 2005, data gaps existed within LexisNexis® and only limited results were found, therefore data from 2005 was omitted from the analysis. In addition, the time of analysis (June 2015) resulted in only 6 months of data for 2015, this year was therefore also omitted from the analysis as it was not representative of a complete year. Please see Appendix 2.3 for detailed methodology.

This analysis indicates that public exposure to messages regarding mBC has been increasing steadily over time (Figure 2.13).

Figure 2.13

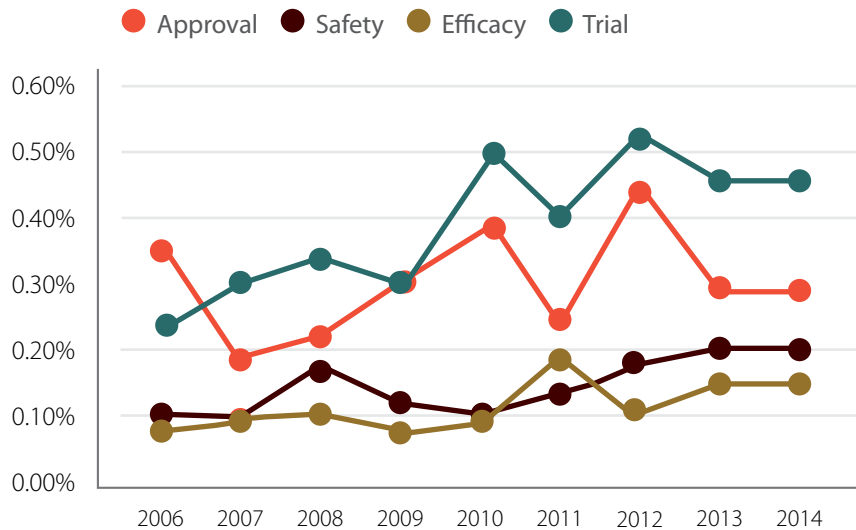
Yearly Distribution of Newspaper Articles and Newswires on mBC Collected from 2006 through 2014

Research from Appendix 2.3



Further analysis of the media coverage on mBC (See Appendix 2.3) shows that the majority of mBC media content focuses on treatments, safety, efficacy and clinical studies (Figure 2.14); the volume of such content has increased slowly with time. Treatment guidelines and quality standards receive less media coverage compared with articles on specific therapies; however, since 2009, there has been an increase in media reports

Figure 2.14
Frequency of the Terms Approvals, Trials, Safety and Efficacy in mBC Media Coverage 2006 through 2014
 Research from Appendix 2.3



focusing on pain and suffering in the context of mBC (Figure 2.15) - this is a small but important step forward in raising awareness.

In the time period of the media analysis conducted for mBC, several milestones have occurred that could have contributed to the increase in media coverage and built a positive momentum (Figure 2.16). These efforts have focused on the unique challenges that mBC patients face.

Figure 2.15
mBC Media Coverage of Palliative Care, Pain, Suffering, Fear and Job Loss from 2006 to 2014
 Research from Appendix 2.3

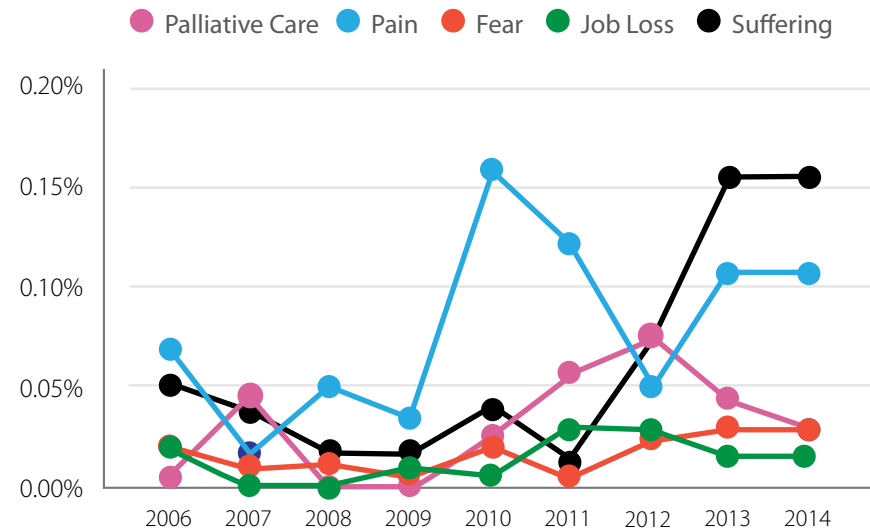


Figure 2.16

| ADVANCEMENT | MILESTONE (examples shown; not a comprehensive review) |
|---|---|
| Recognition of mBC as distinct from early BC | <p>Creation of metastatic breast cancer day on Oct 13 (Huffington Post, 2009)</p> <p>First International Consensus Conference for Advanced Breast Cancer in 2011 (Cardoso, 2012a)</p> <p>Formation of the mBC Alliance in US (MBC Alliance, 2014)</p> <p>Launch of the mBC Alliance Landscape report (mBC Alliance Press Release, 2014)</p> |
| Launch of several high profile initiatives to educate the public and breast cancer community, and spur action on behalf of patients | <p>"Count Us, Know Us, Join Us" (Count Us, Know Us, Join Us, Novartis, 2013)</p> <p>"Here and Now" in Europe (Here and Now Report, Novartis, 2013)</p> <p>"Breast Cancer: A Story Half Told" in the US (A Story Half Told, Pfizer, 2014)</p> |
| High profile mBC patient perspectives and personal stories in the media | <p>As an example, Laurie Becklund, the late Pulitzer-Prize winning journalist, reported her frustrations at the lack of mBC attention, in particular from breast cancer awareness groups themselves . (Becklund, LA Times, 2014) She wrote of the inability to 'count' this patient group or access new treatments in a timely fashion, finally calling for a database to record as much data as possible about this group.</p> |
| Advances in science with positive phase III data or approval of new drugs for mBC patients | <p>New approvals (FDA Hematology/Oncology Approvals)</p> <p>Pertuzimab (NCI pertuzumab, 2015)</p> <p>Ado-trastuzumab emtansine (NCI Ado-trastuzumab emtansine, 2015)</p> <p>Everolimus (NCI Everolimus, 2015)</p> |

“ Contrary to what we often hear, death from breast cancer strikes all ages... from teens upward... This disease deserves strong public attention. It is not a disease of the elderly. It takes too many lives in their prime. ”

“CJ” (Dian) Corneliussen-James, Co-Founder, President, and Director of Advocacy, METAvivor Research & Support, 2015



Although these milestones represent a step forward for mBC, further efforts are required. Most of these activities have been restricted to North America and Europe. Public understanding of mBC remains limited (mBC General Population Survey, Pfizer, 2015, A Story Half Told, Pfizer, 2014); many mBC patients still experience isolation and stigma (MBC Alliance, 2014). Though mBC Awareness Day has brought more focus on mBC, it is one day in an entire month devoted to breast cancer where the emphasis remains on early-stage breast cancer and the need for self-examination and early detection. (National Breast Cancer Foundation, 2015) Further analysis is needed to understand the proportion of media coverage on mBC relative to overall breast cancer media coverage. Even if mBC coverage increases in absolute terms the impact of this difference may be limited if it remains a small fraction of the total media coverage for BC.

Honest, realistic and accurate representation in the media of the experience and outcomes of patients with mBC may enable the wider community to better support both patients and their caregivers. The communication of accurate information is essential in building a shared sense of empathy between patients with breast cancer, regardless of disease stage, as well as with the general public, and is especially important in destigmatizing metastatic disease. Charitable organizations and patient groups provide mBC patients with a global 'voice' through the sharing of personal stories and educational materials, which can contribute to enhanced public understanding of the disease and help reduce the isolation experienced by these patients.

“I think most people don't want to know about metastatic disease because it's scary.”

North American Respondent, mBC PSO Survey, Pfizer, 2015

In October 2015, the US based Metastatic Breast Cancer Alliance launched a social media campaign featuring real patients, #MetastaticSayIt, to educate the public about mBC. (MBC Alliance, 2015) More such efforts are needed across the world to highlight the mBC patient experience, within the appropriate cultural and social context.

Increased media coverage may mobilize public engagement and in turn help spur action amidst policymakers to advance the priorities for mBC. As an example, global research indicates that the extensive media coverage of AIDS and the gaping unmet need for treatments garnered the FDA to seek improved approval processes for these drugs, indicating that public engagement was a driving force to place AIDS treatments on the FDA priority list. (Carpenter, 2002)

Information presented in traditional and social media does influence public perception. However, not all available sources of information are evidence based and misinterpretation is possible. As such, information must be robustly supported by credible data, and communicated in a clear and consistent tone, to effect change in the perception of mBC.



D Cultural perspectives impact the public understanding of mBC and associated health-related behaviors

“People would rather have AIDS than cancer, they know that they can survive AIDS but do not think they can survive cancer... in Zambia, cancer equals death.”

Udie Soko, Co-founder and Executive Director at the Zambian Cancer Society, Zambia, 2015

Regional and local cultural norms drive variations in the public perception of breast cancer and the creation of tailored resources can, in part, shape the public's perception towards mBC, positively affecting patient lives by reducing social stigma and enhancing community support networks. For example, Chinese women are not routinely inclined to check for breast cancer due to the cultural belief that cancer is a punishment and is contagious, and due to the desire to keep personal health matters private. (Beckjord, 2012) A focus group study evaluating attitudes among Chinese women demonstrated that women's attitudes towards breast cancer screening were significantly improved after watching a short video about the process that includes a soap opera and a segment with a physician. The authors argued that creating a culturally tailored video helped in increasing mammography use among Chinese women. (Wang, 2008)

Similarly, in South Africa, there is a reluctance to present with breast cancer symptoms and undergo physical examinations. There is a perceived invasion of privacy associated with the examination, due in part to the social opinion that private areas of the body should not be discussed. (Beckjord, 2012)

In Pakistan, women with mBC often delayed telling their family that they had found a breast lump until it caused them significant pain and anxiety. (Banning, 2009) In Pakistan and Nepal, there is a widely held belief that breast cancer is a communicable disease that can be contracted by touch or contamination. This results in women concealing their diagnosis from their families and spouses, with some opting not to seek care at all. (Banning, 2012; Bhatt, 2011) This level of stigma associated with the disease not only has a negative impact on diagnosis and treatment, but also creates a heavy psychosocial burden on these women.

There is a division between those countries where discussion of the breast is permissible and those where it is not. Those countries, where communication around breast health and breast cancer is more acceptable, demonstrate an evolution in societal norms and culture over time. This evolution reflects 'normalization' of breast cancer through repeated communications. However, it is still necessary to minimize ongoing reluctance to communicate and educate about mBC. It is important to use sustainable community-based avenues, such as community health workers, women's groups, churches, and health facilities to successfully reach women outside of urban areas where women have greater access to education. (Multhoni, 2010; Ford, 2003; Fernandez, 2009) Charities, such as the Uganda Women's Cancer Support Organization (UWOCASO) aim to raise breast cancer awareness to give such a voice to Ugandan cancer survivors. (UWOCASO, 2015)



“[In some African countries], people did not even have a word for breast cancer. They did not know what breast cancer was...physicians would always diagnose infectious diseases first before they said the word cancer because it was not in their [vocabulary]. Since then, there has been increased awareness.”

Dr. Olufunmilayo Olopade, Director of the Center for Clinical Cancer Genetics, University of Chicago, 2015



Marie Pandeloglou, mBC patient, with her mother. Marie is living with the disease.

The use of fear-based messages is unlikely to motivate women to undertake early detection, and instead may intensify their anxiety about the disease (Cancer World, 2013). However a recognition of the severity of breast cancer could be beneficial if it brings about a reduction in stigma and reluctance to communicate about advanced-stage disease. (Cancer World, 2013)

Irrespective of socio-economic status, stigma unfortunately still exists for patients with mBC. More work must be done to help alleviate the burden of stigma on patients and ensure broader, community-wide support for patients with mBC to live with their disease.



Chapter 4: The Impact of Patient Support and Advocacy Organizations in mBC

- A number of Patient Support Organizations (PSOs) have begun to focus more attention on supporting patients with mBC in recent years
- PSOs consider the hierarchical order of needs to be similar between eBC and mBC patients; however, they acknowledge the greater level of support needed for mBC patients
- PSOs spend a lower proportion of efforts on mBC due to several factors including limited resources, perception of relative size of mBC patient population, local needs, logistical and cultural barriers in accessing mBC patients
- Patient advocacy efforts in influencing health policy for breast cancer vary by region
- Peer support networks offered by PSOs are particularly important to mBC patients, but often challenging to implement

In this report the term Patient Support Organization (PSO) is used to describe organizations that offer a range of services to support patients directly (eg, peer support groups, education, information), and/or advocate on their behalf to advance patient care, including policy changes, public education and raising research funding. PSOs are typically charitable or non-profit organizations and may differ widely in scope of operations. PSOs operate in many countries and strive to meet the needs they consider to be the highest priority to the patients and caregivers in their communities. (mBC Patient Support Organization Survey, Pfizer, 2015)

Patient Support Organizations (PSOs) play a vital role in supporting breast cancer patients and their families, providing a wide range of services to meet their evolving needs. Collaborations developed by PSOs have helped to drive common agendas and initiatives to support the mBC community. Such collaborations include the Metastatic Breast Cancer Alliance in the US and the pan-European organization, Europa Donna,

which offers specialist 'sub-groups' to address the unique needs of women with mBC. (mBC Alliance, 2014; Metastatic Breast Cancer: Focus for Advocacy, Europa Donna, 2014)

Based on primary research encouraging trends can be seen in the levels of support and advocacy for patients with mBC, however global variation exists. Although it is recognized that there continues to be issues surrounding appropriate and effective support for patients with mBC, some PSOs have employed concerted efforts in driving change and improvements have been made. In a 2014 survey conducted by a PSO with 17 of its mBC patient members, 11 said that they felt their local breast cancer support or advocacy group adequately met their needs for information and support. Despite a small representation of patients, this was recognized as an improvement on past surveys where a majority had not felt appropriately supported. (Metastatic Breast Cancer: Focus for Advocacy, Europa Donna, 2014)



Methodology: To improve understanding of the needs of mBC patients, and the activities and contribution by PSOs in meeting these needs, a qualitative primary research project was commissioned by Pfizer, that included 50 in-depth telephone interviews, each 45 to 60 minutes in length (some were face-to-face interviews) with key members of PSOs. The countries included were Canada, US, Belgium, France, Germany, Greece, Ireland, Italy, Poland, Spain, Turkey, UK, Australia, China, Japan, South Korea, Argentina, Brazil, Colombia, Costa Rica, Dominican Republic, Mexico, Egypt, Kenya, Rwanda, Saudi Arabia, Uganda, and Zambia.

Respondents were PSO leaders (CEOs, Presidents, Directors, etc.) of charitable and non-profit organizations that focus on mBC, breast cancer, and/or cancer on a local, national, and global level. They were selected to participate in the survey on the basis of their strategic and/or program responsibilities and their involvement in directing, developing, and/or managing health education, outreach, evaluation, and/or outcomes for their organization. On average, the tenure of respondents within a specific PSO is 8 years, with a range of 1 to 20+ years.

The surveyed PSOs vary greatly in size, with the number of employees and volunteers ranging from 2 to 1500+; the average staff size was under 20. The number of years surveyed PSOs have been supporting the needs of the breast cancer community also vary, ranging from 1 to 50+ years with an average of 11.5 years. (mBC Patient Support Organization Survey, Pfizer, 2015)

Field interviews were conducted from June 15, 2015–August 3, 2015.

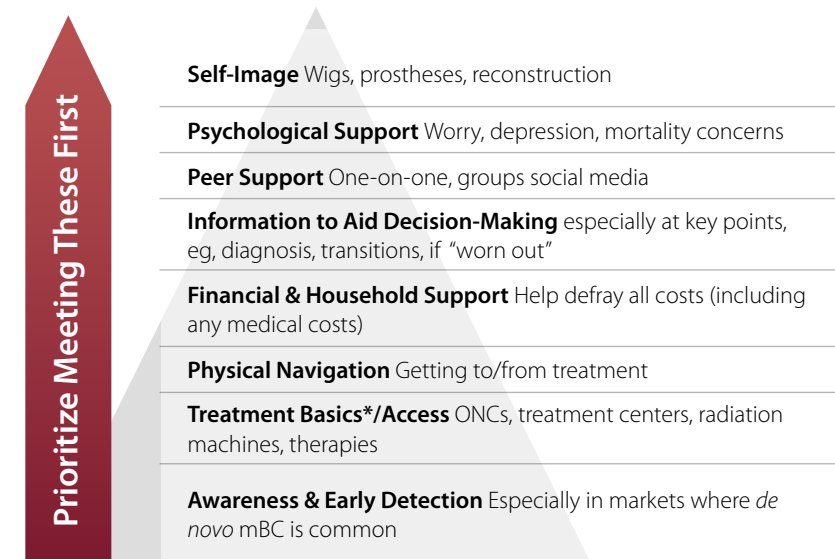
A PSOs acknowledge the greater support needs of mBC patients, but prioritize them differently depending on available resources and local needs

The PSOs surveyed highlight a hierarchy of patient needs that exist for patients with breast cancer or mBC, and that more basic needs (awareness of breast cancer, self-examination, detection, access to treatment and availability of physicians to provide treatment) must be met before “higher-level” needs can be addressed (psychological support, aids to decision making, aids for improving self-image) (Figure 2.17).

Figure 2.17

Hierarchy of Needs Across All Stages of Breast Cancer, as Perceived by PSOs

mBC Patient Support Organization Survey, Pfizer, 2015



* In some countries, such as the US, reconstruction is considered as a basic treatment

** The hierarchy does not suggest relative importance, provision of services, nor utilization of services, but instead provides an overlay that applies in context where needs are met as well as where they are not.



Generally, PSOs consider that relative to one another, eBC and mBC patient needs are similar. This is reflected by consistency in the hierarchical order of needs for both eBC and mBC patients. However, the extent of those needs does differ between early and metastatic disease. PSOs report that patients with mBC have much greater need in terms of psychological support, financial support and access to services, compared with those patients who have earlier-stage disease. While stage (especially eBC vs. mBC) is an important driver of needs, other factors also shape this; one crucial differentiator highlighted was de novo vs recurrent diagnosis of mBC. Others include diversity of patients in terms of personality, desire for information, and course of illness. (mBC Patient Organization Survey, Pfizer, 2015)

While acknowledging the needs of mBC patients, PSOs report that a lower proportion of their efforts are directed towards mBC within BC overall. A range of barriers impact PSOs ability to meet patient needs, especially in mBC; these include; perception of mBC patient population, perspective on mBC needs, cultural factors, and logistics.

PSOs report that the proportion of funding between eBC and mBC is often dictated by the size of the patient population. PSOs perceive mBC as a smaller patient population and it therefore receives a proportionately smaller share of support. This perception of PSOs is challenged by the reality that in some parts of the world, such as developing countries, 50%-80% of patients are being diagnosed with advanced disease. (Unger-Saldana, 2014)

PSOs report that patients with mBC have much greater needs in terms of psychological support, financial support and access to services, compared with those patients with earlier stage disease.

(mBC Patient Support Organization Survey, Pfizer, 2015)

PSO services specifically focused on mBC patients are not only dependent on the available funding, but also on local need and therefore regional variation in provision of support services can be seen (Figure 2.18).

Awareness and education is frequently offered to both general BC and mBC patient populations, however awareness, though among the top services provided, is relatively less frequently offered for mBC (>90% vs 60%-69%). Most PSOs surveyed reported that they offer peer support for mBC patients. In North America, peer support is offered to the general BC population by approximately 50%-75% of PSOs; however, this is not a frequently offered support service for mBC patients. (mBC Patient Support Organization Survey, Pfizer, 2015)

One way for PSOs to effectively support the mBC population is in the specialization of services; a “complete, don’t compete” approach is taken, that yields complementary services rather than those that compete

// The women who are living with metastatic breast cancer are getting 100% of our programs, but the numbers are smaller. If we have 4500 callers and peer supporters, maybe we are talking about 70 women [who are mBC patients]. //

North American Respondent, mBC PSO Survey, Pfizer, 2015



Figure 2.18

Most Frequent Activities Provided to Support Patients with mBC

mBC Patient Support Organization Survey, Pfizer, 2015

■ Most frequently offered activities for patients with mBC by region

| Activities Engaged in to Support mBC | US and Canada (n=11) | Europe (n=14) | Asia Pacific (n=7) | Latin America (n=10) | Africa and Middle East (n=8) |
|--------------------------------------|-------------------------|------------------|-----------------------|-------------------------|------------------------------------|
| Awareness | | | | | |
| Patient Education | | | | | |
| Treatment Education | | | | | |
| Access Advocacy | | | | | |
| Peer Support | | | | | |
| Supporting Pts to Become Adv. | | | | | |
| Policy Advocacy | | | | | |
| Financial | | | | | |
| Data Generation | | | | | |
| Raising Awareness for Sci. Res. | | | | | |
| Clinical Trials/Registries | | | | | |
| Regulatory | | | | | |
| Legal | | | | | |
| Funding Scientific Research | | | | | |

This table represents the most frequently provided services only. Activities not highlighted are still offered across regions based on survey responses with the exception of policy and regulatory support in Asia/Australia and funding for scientific research in the Africa/Middle East region. The criteria for which activities are classified as 'most frequent' varies by region.

against other organizations. Each organization can vary in size, scope, reach, and mission, and as such the goal of overcoming barriers to meeting mBC needs should not be pursued at the expense of making PSOs homogeneous. (mBC Patient Support Organization Survey, Pfizer, 2015)

“If there are other organizations doing [something], we’re not going to recreate the wheel. We’d rather just direct them to other organizations that are... the best fit for their needs.”

North American Respondent, mBC PSO Survey, Pfizer, 2015



B Peer support networks offered by PSOs are particularly important to mBC patients, but often challenging to implement

“There are many women who have to face the disease again as recurrent or with metastases in another part of the body. If they have a recurrence, we just lose them. We don’t know where they are. They feel that they are not the ‘winners’ anymore, so they withdraw from the whole group.”

European Respondent, mBC PSO Survey, Pfizer, 2015

One of the key services that PSOs provide BC patients is peer support networks. For mBC patients, peer support is of particular importance in the context of the emotional challenges and social isolation they experience, as outlined in Section 1: *Patient Care Perspectives*. Evidence demonstrates that online support groups offer women with mBC the feeling of being supported by one another, even though they may not have met face-to-face. Online support groups also served as a place for information exchange, making women more active in their treatment decisions, and reducing ambiguity about new symptoms. Group cohesiveness benefits were seen in the women. Peer support groups directly alleviated their anxiety, helped them gain better medical care, reduced their need for social support, and increased their openness to others. Participation in such peer networks also reduced the sense of isolation that women feel, as they often feel partners, friends, and relatives are not able to completely understand what they are going through. (Vilhauer, 2009)

Studies have shown that stage-specific groups are more helpful to women with mBC than mixed-stage groups (ie, those that include both eBC and mBC patients), also seen via online support groups. (Vilhauer, 2009; Vilhauer, 2011) This is often because of the unique experiences a patient with mBC is living through; mBC onset (de novo vs recurrent), progression (indolent vs aggressive), symptoms experienced, and treatment goals are all individualized to a greater extent vs eBC patients. Some PSOs also reported that eBC patients were reluctant to be in the same peer groups as mBC patients. (mBC Patient Organization Survey, Pfizer, 2015)

“Up until now [with the eBC patients] we were trying to break the stereotype or notion that ‘breast cancer means death.’ It took us a lot of time to deal with that. When it comes to metastases, everything is going back to the beginning—patients hear ‘metastases’ and they think it means painful death. That’s the way people here think about metastases.”

European Respondent, mBC PSO Survey, Pfizer, 2015

Despite the rationale and clear benefit of providing peer support for mBC patients, PSOs admit that true peer support is difficult to achieve. Barriers include a reluctance by mBC patients to participate, a wish not to build their identity primarily on mBC, and a lessening of activity overall. In addition, mBC peer group members may find it traumatizing if their mBC peers progress or pass away. (mBC Patient Organization Survey, Pfizer, 2015)

“We are shutting down [our mBC group] after 7 years....because it is too painful when someone dies.”

North American Respondent, mBC PSO Survey, Pfizer, 2015



© Patient advocacy efforts in influencing health policy for breast cancer vary by region

Patient advocacy can also have a significant influence on policy decision-making. (Lerner, 2002) In high-income countries, improvements in breast cancer care have been achieved as a result of efforts by patients and their supporters, as well as survivors, the healthcare industry and media. (UICC, Planning Comprehensive Breast Cancer Programs) In countries where patient advocacy groups devote attention to breast cancer, these efforts have successfully increased awareness of mBC and contributed to increased access to cancer screening, diagnosis, and treatment. (Here & Now, Novartis, 2013)

PSOs are involved in the development of health policy at both the local and national levels. This involvement includes increasing policy-maker awareness of patient and caregiver needs through educational programs, receptions, and one-to-one meetings with specific government officials.

- In the US, the National Breast Cancer Coalition (NBCC) launched “Breast Cancer Deadline 2020” - a call to action for policymakers, researchers, breast cancer advocates, and other stakeholders to know how to end the disease by 2020 (Breast Cancer Deadline 2020)
- Komen listed amongst its 2015 advocacy priorities the identification of expanded US federal funding for breast cancer research and policies that improve insurance coverage of breast cancer treatment; including, support for legislation that creates parity in insurance coverage for oral medicines compared with intravenous treatments (Susan G. Komen, National Public Policy)
- In Europe, Europa Donna is actively engaged in advocating for the European Parliament Written Declaration of Breast Cancer and other national parliamentary lobbying projects in EU member countries to raise awareness of the needs of mBC patients in policy and in BC guidelines (EuropaDonna.org)

- Patient surveys carried out by the Breast Cancer Network Australia have identified both the support and information needs of patients with mBC and brought existing policy gaps to the attention of health decision-makers around workplace issues, access to superannuation, breast care nurses, and supportive care. (BCNA Survey, 2015) At the Georgetown University Lombardi Comprehensive Cancer Center in the US, the Georgetown Breast Cancer Advocates group are critically involved in research project decisions including grant approvals, ensuring all projects are patient-centered (Brundage, 2015)

For more information on PSO involvement with policy initiatives, please refer to Chapter 1: *Health Policy for mBC*.

Figure 2.19

PSO Provision of Policy Advocacy Services by Region

mBC Patient Support Organization Survey, Pfizer, 2015

| Region | BC general | mBC specific |
|--------------------|------------|--------------|
| North America | 82% | 45% |
| EU | 86% | 57% |
| Latin America | 70% | 70% |
| Africa/Middle East | 29% | 38% |
| Asia/Australia | 75% | 0% |

When comparing the PSO's perceived needs of mBC patients vs reported activities, policy was identified by PSOs as an area where there is a gap in activity.

(mBC Patient Organization Survey, Pfizer, 2015)



Provision of policy advocacy services by PSOs also varies according to region (Figure 2.19). When comparing the perceived needs of mBC patients and the reported PSO activities, policy was identified by PSOs as an area where there is a gap in activity in most regions. Where although between 70-89% of PSOs engage in breast cancer policy support, less than 60% engage in the same activities specifically for mBC patients. (mBC Patient Support Organization Survey, Pfizer, 2015)

The PSO advocacy efforts to influence health policy are tailored to region-specific or local challenges. In developing countries such as Africa, PSOs need to address basic infrastructural issues, such as access to radiotherapy and pain medications before specific mBC issues are approached. For example, a framework piloted in Japan and South Africa has been designed to assist advocacy organizations in effecting change for patients with cancer in general and indicated that immediate support through advocacy groups and patient forums are just as essential as long-term effects on policy. (Scheer, 2015)

Many PSOs are actively involved in supporting access to cancer medications and reimbursement coverage for all necessary tests and treatments.

Many PSOs list “making the patient voice heard” as one of their principal goals. (mBC Patient Support Organization Survey, Pfizer, 2015) Despite being a key area of focus for many PSOs, creating opportunities for the

elevation and vocalization of the patient voice to policy makers can be challenging, especially in low- and middle-income countries. Instability in the political infrastructure, a lack of fiscal or human resources available to lead advocacy efforts, socioeconomic or educational status can limit an individual’s ability to effectively advocate for themselves or others. (UICC, Planning Comprehensive Breast Cancer Programs) However, effective mBC advocacy is possible in low- and middle-income countries. For example, in Nigeria, a campaign was conducted to raise awareness at all levels of government, of the need to subsidize cancer treatment as a strategy to reduce the incidence of mBC. (Adisa, 2011)

A multi-stakeholder approach to developing advocacy efforts has demonstrated impact in raising awareness of breast cancer in high income countries. (UICC, Planning Comprehensive Breast Cancer Programs) Learnings can be taken from coordinated approaches to help guide policy makers towards implementing change. (UICC, Planning Comprehensive Breast Cancer Programs)

PSOs play a critical role in defining the mBC patient experience. While it is encouraging that progress has been made, and PSOs recognize the unique needs of mBC patients, barriers to providing optimal support remain. Through achieving a better understanding of the current disease state and the role of PSOs, further progress in the provision of tailored and compassionate support to mBC patients can be made.

“The goal of many PSOs is to make sure that the voices of women living with metastatic BC are heard during Breast Cancer Awareness Month because so much is going on and most of it relates to early-stage: ‘Let’s look for a cure.’ ‘Treatment is better.’ ‘Diagnosis is better.’ But there’s still a large number [of patients] who are becoming metastatic.”

North American Respondent, mBC PSO Survey, Pfizer, 2015



Chapter 5: Workplace Perspectives for mBC Patients

- **Issues affecting work and employment remain relevant to patients with mBC and their caregivers**
 - There are financial and psychological advantages to returning to work after a diagnosis of mBC, but staying in work can be difficult
 - Fatigue, persistent treatment-related adverse effects, and emotional ill-health can also increase the risk of not being able or allowed to work
- **In some countries, employees with cancer are protected in the workplace by disability equality legislation**
 - Where such legislation exists, employers are required to make reasonable accommodations to the work environment that prevent discrimination against employees with cancer
- Individualized accommodations as well as the support of colleagues and co-workers are important factors in facilitating return to work
- Despite this, the employment experiences of patients with mBC are variable
- Line managers need more training, support, and resources to facilitate return to work and employment retention for employees with cancer
- **More research is required to identify the specific needs of employees with mBC**

People continue to live their lives during all the events that surround a diagnosis of mBC, the demands of treatment, and the eventual preparations for the end-of-life. A diagnosis of mBC may occur when patients are active in the workplace and this brings specific challenges to both employees and employers.

All cancer survivors have a significantly increased risk of unemployment and are less likely to be re-employed than those without cancer. (Mehnert, Cancer, 2010) Cancer patients described worrying about the effect of their diagnosis on career opportunities and losing their job. (Cancer Council, Victoria, 2013) Attendance at doctors' appointments or the side effects of treatment necessitate workplace absence. However, the need to take

time off is associated with communication and relationship difficulties between employer and employee. (Cancer Council, Victoria, 2013) In a UK survey of 370 line managers from public sector, private and small-to-medium enterprises, respondents tended to be ambivalent about hiring and retaining people with cancer; a finding that brings significant implications for those wanting to return to work with the same or a different employer. (Amir, 2010) Also in the UK, the creation of the Health and Work Assessment and Advisory Service, working in conjunction with the Department of Work and Pensions, is anticipated to support return to work for people with cancer by providing occupational health advice to employers and employees. (Taskila, 2013)



Methodology: To understand the workplace experiences of mBC from the perspectives of both the employee and employer, a literature review was conducted on research into the impact of mBC, on work published within the past 10 years. See Appendix 2.4 for more details on the literature search methodology. Additionally, a 90-day snapshot of online sources was analyzed for discussion about employment matters for patients diagnosed with mBC. See Appendix 2.5 for details on the LexisNexis© search.

Note that the majority of published data on the impact of cancer on work generally, and mBC specifically, has been collected from Europe and the United States; data from low- and middle-income countries is scarce. Therefore, more research is required to understand the impact of mBC on employment in these countries as it would be incorrect to assume that experiences are the same in other regions. (Islam, 2014) Additionally, while the rates of return to work are relatively well documented, few studies have shed light on keeping a job, absences, and the workplace experience from the perspective of the patient, caregiver, or other stakeholders such as employers and co-workers. (Nitkin, 2011) Existing data does show that access to paid employment remains relevant to those with mBC. (Corneliussen-James, 2011)

A Work and employment

Work outside of the home has variable importance in countries and cultures around the world. Gender equality, including participation, remuneration and advancement in work, has a positive correlation with per capita GDP, and female participation in the global workforce has increased over the past decade. (Schwab, 2015; OECD.stat) Having more women in the workforce benefits the social status and economic opportunities of the next generation of women; they invest a large proportion of household income into the education of their children. (Aguirre, 2012)

A survey of an international population of patients with mBC found that half of all respondents with mBC who returned to work made the decision to leave within one year.

(Corneliussen-James, 2011)

A diagnosis of mBC occurs in adults of all ages, including those of working age. (SEER.cancer.gov) The increasing number of treatment options available means that patients with mBC can receive medication for a prolonged period of time. Many with mBC who are in employment choose to return to work after their diagnosis. This can be for financial and emotional reasons. Despite a desire to continue working, challenges remain for employees with mBC and staying in work can be difficult. A survey of an international population of patients with mBC found that half of all respondents with mBC who returned to work made the decision to leave within one year. (Corneliussen-James, 2011)

B Maintaining employment provides psychological, economic and societal benefits to patients with cancer and their caregivers

The (re-)integration of people living with cancer into working life is an important aspect of social functioning, according to the International Classification of Functioning, Disability and Health. (WHO.com) Return to work is associated with a return to normal activities, social recovery and rehabilitation after cancer treatment, improved well-being and a reconnection to normal life. (Islam, 2014; CBCN, 2010; Yoon-Jung, 2013) Work can also provide a distraction from illness or treatment, by keeping busy and occupying the mind. (Appendix 2.5; CBCN, 2010). Moreover, employees with mBC recognize their colleagues and co-workers as a source of support. (Appendix 2.5, Nassau Guardian, 2015)



In those with advanced cancer, employment has been associated with an improvement in well-being compared with unemployment. (Zimmerman, 2011) Employment may also improve adherence with cancer therapy. Adherence to treatment such as radiotherapy has been shown to be greater in those who are employed than the unemployed or retired, although the reasons are unclear. (Fyffe, 2010)

In those with advanced cancer, employment or retirement has been associated with an improvement in well-being compared with unemployment. (Zimmerman, 2011)

There are studies into the needs of caregivers of patients with advanced, serious illnesses, including cancer, respiratory disease, motor neuron disease, heart failure, and end-stage renal failure. They have found that while some caregivers would like to give up work and provide full-time support to a relative with serious illness, others find that continuing to work provides an important coping strategy. (Gysels, 2009) Furthermore, unemployment in caregivers can significantly increase family strain when caring for patients at the end-of-life, compared with being employed. (Yoon-Jung, 2013; CBCN, 2010)

“The girls at work made a rota (schedule) take turns in picking me up from work as dad (my husband) was working late.”

90 Day Social Media Snapshot (See Appendix 2.5)



© Financial burden of treatment or medical insecurity can often drive patients with mBC to return to work

In countries where there is no national health system or a mixed public/private health service, being out of work may leave patients financially vulnerable to treatment costs. (Corneliussen-James, 2011; Timmons 2013) Although not specific to cancer, a systematic review of the direct and indirect costs of illness in low- and middle-income countries found the total economic cost of illness for households was frequently above 10% of household income, a threshold defined as “catastrophic” to the maintenance of the home; and occurring precisely at a time when domestic income is reduced. In situations like this, the family may engage in a number of coping strategies including: taking on additional employment, selling assets such as land or livestock, reducing the use of resources, including food, and borrowing money from friends, family or moneylenders. (McIntyre, 2005) In high income countries, health insurance and money worries are among the top sources of distress in patients with mBC. (Buzaglo, 2014; Breast Cancer Center Survey, Pfizer, 2015) In a systematic review of studies from 11 countries in Europe, Southeast Asia, USA and Canada, access to employer health insurance coverage or other work-related benefits, including extended sick leave or disability pensions, were identified as important influences in the decision to return to work. This finding highlights the impact of support, financial burden or fear of being unable to access affordable medical treatment in employment-related decision making. (Islam, 2014) In a separate Canadian study of 446 patients with breast cancer, one-fifth reported returning to work before they were ready, as a result of financial pressures. (CBCN, 2010)

In a Canadian study of 446 patients with breast cancer, one-fifth reported returning to work before they were ready, as a result of financial pressures. (CBCN, 2010)

Breast cancer, at any stage of diagnosis, has a serious impact on working for those who are self-employed. A lack of job security, access to employer benefits, or being unable to meet contractual commitments causes great stress. Better support is required for those who are self-employed, through, for example, extending social security or disability benefits currently available only to employees. Alternatively, it has been suggested that work-related insurance suitable for self-employed workers should be in place. (CBCN, 2010)

In many countries around the world, once employee sick leave benefits have ended, some mBC patients face the challenge of maintaining their financial contribution to the household through social security. These national benefits are mostly set at a significantly lower level than their salary. (OECD, 2011) In Canada, some patients also describe experiencing poor advice, or unrealistic expectations from social security staff. (CBCN, 2010) The situation for those patients who had a fulltime role as a homemaker prior to their diagnosis is often just as difficult. The impact of mBC may impair a patient's ability to fulfill their usual roles and responsibilities at home and require home help to be hired. As the patient is not employed, they are unlikely to be eligible for work related benefits, for example early employment insurance support, and therefore be put at a further financial disadvantage. (CBCN, 2010)

Families and caregivers of patients with mBC are also directly affected. Caregiving increases the risk of unemployment. (Girgis, 2013) For those caregivers who continue to work, the demands of caring for a loved one with mBC may require periods of time away from the job, giving up education or taking on overtime or part-time employment to maintain the household income. (Wan, 2012; Mazanec, 2011; CBCN, 2010; Mayer, 2015) Any reduction in paid work contributes towards caregiver social isolation and, beyond the immediate economic impact to the household, also has long-term financial consequences arising through a loss of savings for retirement. (Girgis, 2013)

D Employees with mBC face specific challenges arising from their cancer and treatment when considering return to work

Significant differences in the experience of returning to work have been described by those with eBC compared with mBC. In a multicenter US survey of 730 patients aged less than 40 years, most young women with eBC remained in employment at one year following their diagnosis. Many reported that if an accommodation to their work environment was required, their employers were, on the whole, happy to make such an adjustment. Their disease did not limit their ability to work, and 74% were satisfied with their employment. (Rosenberg, 2015) In contrast, patients with mBC from many other regions around the world described their advanced disease as a barrier to returning to work. This was particularly the case when their role was manual, stressful or they considered it of low importance. (Islam, 2014; Tevaarwerk, 2010; Mehnert, Cancer, 2013) The research did not identify specific reasons why advanced disease negatively impacts return to work, but they are likely to arise from the consequences of treatment, as well as individual- and job-related factors.

Patients with mBC from many regions around the world described their advanced disease as a barrier to returning to work. This was particularly the case when their role was manual, stressful or they considered it of low importance.

(Islam, 2014; Tevaarwerk, 2010; Mehnert, Cancer, 2013)

In addition to the stage of disease, other factors that increase the risk of not being able, or allowed to work, include type of work, ethnicity, age >45, ongoing therapy, acute and delayed adverse effects of treatment, poorer



performance status, fatigue, lymphedema, mental and emotional health, and cognitive limitations. (Tevaarwerk, 2010; Mujahid, 2011; Nitkin, 2011; Islam, 2014; Valdivieso, 2012; Mehnert, Scand J Work Environ Heal, 2010; CBCN, 2010; Blinder, 2012) Some of these other factors are more commonly experienced by patients with mBC. (Yin, SABCS, 2015)

“Undergoing treatment while working is challenging. I was the manager of an accounting department, and sometimes I’d be in the middle of something at work and would need to leave to get to the [hospital]. I was lucky that I had a very understanding supervisor.”

90 Day Social Media Snapshot (See Appendix 2.5)

Indeed, breast cancer progression and treatment is associated with a lower probability of employment compared with those whose disease has not progressed, and may also result in reduced work productivity through more missed hours at work, compared with earlier stages of the disease. (Yin, SABCS, 2015) In a cohort of 2,013 Swedish and Dutch patients with breast cancer, nearly a quarter of whom had a diagnosis of mBC, 40%-41% and 69%-72% described absence from employment and reduced ability while at work respectively. (Frederix, Clinical Therapeutics, 2013) The consequences of cancer and its treatment include cognitive, physical and emotional challenges. (Feuerstein, 2006; CBCN, 2010) Furthermore, the type of therapy received also affects ability or confidence at work. Those taking hormonal therapies are more likely to be currently employed than those receiving chemotherapy. Treatment with chemotherapy is also more likely to result in caregivers taking time off from work. (CBCN, 2010) Moreover, the extent of surgery and consequences of radiotherapy may limit physical functioning and the ability to carry out some tasks at work. (Jerusalem, 2014; Mujahid, 2010; Islam, 2014)

E Experiences of returning to work following a cancer diagnosis are variable

Employment law in some countries requires employers to make reasonable accommodations or adjustments for those with disabilities. (American Cancer Society, ADA; Macmillan, 2013; Chief directorate of labor relations – South Africa; Government of Canada; Rozman, 2009) The term disability can include cancer, but definitions are different between countries and do not always cover chronic illnesses. Implementation of legislation can also differ among countries and exemptions exist, for example, for small businesses employing few staff. (Association of European Cancer League, 2005; Government of Canada) The Association of the European Cancer League has proposed key areas for consideration that offer basic protection for workers with cancer when incorporated into legislation, policies and work-based tools. These key areas include recommendations for basic protection of employees (particularly vulnerable groups at greatest risk for work termination), maintaining employment and finding new work, the workplace, and caregivers or family members. (Association of European Cancer League, 2005)

The Association of the European Cancer League has proposed key areas for consideration that offer basic protection for workers with cancer when incorporated into legislation, policies and work-based tools.

(Association of European Cancer League, 2005)



The experiences of those returning to the workplace after a diagnosis of mBC are variable and suggest limited formal employer governance about managing employees with cancer. In a UK survey of 219 Chartered Institute of Personnel and Development (CIPD) member organizations, only one-third reported having a good understanding of cancer and the impact of treatment in the workplace. Although cancer-specific policies may not be in place, as described by 73% of respondents, (Cancer Backup, CIPD and Working with Cancer, 2006) in many places they are instead covered by national or organizational policies and procedures designed to protect workers with long-term medical conditions. The UK National Health System provides advice to employers about supporting employees who have chronic health issues. (NHS Choices) In any case, some employees with a diagnosis of cancer describe being well supported by their employers/co-workers and describe examples of the supportive practices offered. (Cancer Council, Victoria, 2013; CBCN 2010; CEW, 2016) These include:

- Physical adjustments to the work environment
- Time off routinely granted for hospital appointments
- A supervisor who has discretion to allow an early finish on days where fatigue or other symptoms are causing a problem
- Discussion about the employee's preference for disclosure and communication with co-workers
- An annual leave bank where fellow employees can donate unused days off for use to employees going through major health or personal situations

In a UK survey of 219 Chartered Institute of Personnel and Development (CIPD) member organizations, 73% of respondents did not have a formal policy in place for managing employees affected by cancer.

(Cancer Backup, CIPD and Working with Cancer, 2006)

In Canada, patients with cancer say public services and large organizations offer greater assistance to those returning to work than smaller companies (defined as those employing less than 50 employees). (Nitkin, 2011) It has been proposed that a collaborative approach between medical personnel, employees and employers in preparation for reintegration into the workplace combined with employer accommodations may have a positive impact on return to work for people living with a cancer diagnosis. (Nitkin, 2011) The key adaptations which help people to return to work are (Nitkin, 2011; Cancer Council, Victoria, 2013; CBCN, 2010; Cancer+Careers.org):

- Flexibility and some discretion over working hours, duties, or location of work
- A gradual or step-wise return to usual working hours
- A supportive work environment including appropriate disclosure to colleagues
- Desk-based rather than manual or service jobs
- Counseling and rehabilitation
- Access and involvement of occupational health support



Note that the literature search did not identify any published research into the factors which support a return to work specifically for employees living with a diagnosis of mBC, but instead focused on cancer survivors, including those with earlier stages of breast cancer. However, data are still being generated. CanWork, a network of researchers from 10 institutions in the UK and Ireland, established in 2011, is coordinating and driving forward research into the employment experiences of patients with breast and other cancers. (Amir, 2011) In the USA, research is ongoing to explore any differences and similarities between the workplace issues experienced by patients with mBC and those with eBC. It is likely that given the differences in treatment goals and the care pathway, the situation for employees with mBC will be more complex. (Interview with Dr. Victoria Blinder, Memorial Sloan Kettering, 2016)

In recognition of unmet support needs for patients with breast cancer in Japan, psycho-oncologists in collaboration with nurses, medical social workers and a legal advisor created a “work ring”. This group provided advice on working status and practical work related issues to patients with breast cancer to ensure they were able to maintain their presence in the labor force. Following a successful pilot, this approach is being rolled out across Japan. (Yamauchi, 2013)

Many employers and medical practitioners are not educated about the impact of mBC and its effects on work. A UK survey found line managers need more training, support and resources to enable them to fulfill their duty of care to employees with cancer. (Nitkin, 2011; Yamauchi, 2013; Interview with Dr. Victoria Blinder, Memorial Sloan Kettering, 2016; Amir, 2010) It can be difficult for an employee to explain and predict the patient journey and timeframe associated with mBC to an employer, and indeed even an educated opinion, may prove inaccurate. Some with mBC may be able to work for many years, but the period of wellness is much shorter for most. (Interview with Dr. Victoria Blinder, Memorial Sloan Kettering, 2016) In periods where the demands of treatment are less obvious, those living with mBC can be

“I wrote a letter to a patient’s supervisor explaining why she needed to sit instead of stand. It was a small thing. A stool. Now she can go to work and sit at the stool and be comfortable not have to worry about losing her job.”

Dr. Victoria Blinder, Memorial Sloan Kettering, 2016

A UK survey found line managers need more training, support and resources to enable them to fulfill their duty of care to employees with cancer.

(Nitkin, 2011; Yamauchi, 2013; Interview with Dr. Victoria Blinder, Memorial Sloan Kettering, 2016; Amir, 2010)



seen by their employers and colleagues as “normal now” and may find it challenging to have their needs for work accommodation or medical appointments accepted. (National Institutes of Health, 2014; Sortor, 2016)

In periods where the demands of treatment are less obvious, those living with mBC can be seen by their employers and colleagues as “normal now” and may find it challenging to have their needs for work accommodation or medical appointments accepted.

(National Institutes of Health, 2014; Sortor, 2016)

When an employee with mBC experiences disease progression that requires changes to their treatment plan, they may need their employer to consider changes to any accommodations that have already been made. For example, if an employee is taking an oral treatment for mBC they may only need one doctor visit per month. If their treatment then changes to a combination of intravenous chemotherapies they are likely to need more hospital visits. Despite limited understanding, employers will also need to be empathetic and consider that despite “looking well” employees with mBC may still be experiencing adverse effects of treatment. Symptoms such as peripheral neuropathy and fatigue, commonly caused by mBC therapy, are not visible but can be long lasting and will impact the daily lives of employees experiencing them. (Interview with Dr. Victoria Blinder, Memorial Sloan Kettering, 2016)

Employees say that patient information about access to work or disability benefits is often lacking. (Cancer Council, Victoria, 2013) In a pilot study in the Netherlands, half of occupational health physicians questioned reported that the provision of an educational leaflet with a treatment plan letter, given to the patient prior to their return to work, was helpful to both the patient and employer; the majority of employees living with cancer adhered to the steps of advice in the booklet. (Nieuwenhuijsen, 2006) Organizations such as Cancer and Careers and Workplace Transitions in the United States, Macmillan Cancer Support in the United Kingdom and the Danish Cancer Society have produced a series of resources to support employees, employers and co-workers in managing the consequences of living with a cancer diagnosis and treatment in the workplace. (Cancer+careers.org; workplacetransitions.org; macmillan.org.uk; Olgod, 2007) Such resources aim to provide practical, targeted support and are readily accessible online.

Despite limited understanding, employers will also need to be empathetic and consider that despite “looking well” employees with mBC may still be experiencing adverse effects of treatment.

(Interview with Dr. Victoria Blinder, Memorial Sloan Kettering, 2016)



Discrimination has also been described by employees with BC, such as reduced hours, changes to role, demotions and work termination. (Cancer Council, Victoria, 2013; Nitkin, 2011; CBCN, 2010) However, evidence from Australia suggests that cancer patients infrequently report discrimination. (Cancer Council, Victoria 2013) Unfortunately, the reaction of work colleagues can also be negative, with co-workers often unsure of how to approach and talk to their colleague with cancer. In one survey, about 25% of workers expressed concern that they would be expected to pick up the slack from a colleague returning from cancer treatment. (Nitkin, 2011)

In one survey, about 25% of workers expressed concern that they would be expected to pick up the slack from a colleague returning from cancer treatment.

(Nitkin, 2011)

In conclusion, patients with mBC choose to return to work for both financial and emotional reasons. (A Story Half Told, Pfizer, 2014) However, existing data is limited as to the specific employment needs of employees with mBC who intend to return to work. The consequences of treatment for mBC result in emotional, physical and cognitive changes that employers need to be aware of when supporting an employee with mBC returned to work.



Chapter 6: The Impact of mBC on Patient Social Relationships and Caregivers

- Patients with mBC try to protect themselves from the societal opinions expressed by the general public about their disease, by limiting contact with or ignoring the views of those outside of their social network
- The dichotomous public opinion of mBC as either a hopeless diagnosis, or one which can be beaten and cured, leaves patients in despair with a diminished sense of hope, frustrated and inhibited to share their own fear
- Interpersonal relationships with caregivers and those close to patients with mBC are critical to the patient's sense of well-being
- Those with mBC describe friends, family, and their spouse or partner, as their best source of support and help with coping
- Caregivers feelings about the situation are complicated, and they find the role can be both positive, but also stressful
- However, caregiver support needs are often overlooked
- Strategies are needed to identify and meet the psychosocial, occupational and financial needs of caregivers surrounding the challenges of balancing work, commitments at home and caregiving

Patients with mBC experience a wide range of physical and emotional symptoms that require additional support, both directly and indirectly, as a consequence of the effect of cancer and its treatment. (Hasson-Ohayson, 2010; mBC Patient and Caregiver Qualitative Research, Pfizer, 2016) Although the interaction between support and coping is complex, the presence of a feeling of support is associated with hope among adults with advanced cancer. (Hasson-Ohayson, 2010; Hasson-Ohayson, 2014) Patients want to maintain their identity for as long as possible and are concerned about the financial, emotional, and practical burdens arising from prolonged treatment for mBC. They describe that, emotionally, the best support boosts their moral; it helps them to stay positive but realistic, keep strong, and doesn't deny their struggles but allows them to express the emotions that they are feeling. The demands of caregiving are far-reaching and must not be underestimated, as spouses, families, and friends feel the repercussions of a diagnosis of mBC in a loved-one. Family caregivers are known to provide a vital role in caring

for patients with mBC, but their understanding of the disease is often fairly limited at the time of diagnosis. (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016)

Qualitative interviews with 28 patients and caregivers were carried out to inform this chapter. The aim of this primary research was to explore the interactions between patients with mBC and members of the general public. The results showed that the quality of interpersonal relationships with caregivers and those close to patients with mBC are critical to the patient's sense of wellbeing. Furthermore, the research confirmed that attitudes about mBC, particularly in developing countries, are still extreme; the diagnosis is seen as either a hopeless situation or something that can be beaten and cured. As a result, patients with mBC either ignore the views of the general public or limit contact with people outside of their support network in an attempt to avoid thoughtless comments or misperceptions about the disease. (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016)



Methodology: To obtain a greater understanding of the personal experiences and perspectives of mBC patients and their caregivers, before and after a diagnosis, 28 individual, 60-minute telephone or face-to-face interviews were conducted from January 6 to 29, 2016. Responses were sought from 14 patients and 14 caregivers from US, UK, Turkey, India, Egypt, Brazil, and Mexico. Findings were analyzed qualitatively to identify key themes and differences across these 7 countries. Additionally, a qualitative review of published research on the support needs of patients and caregivers was undertaken. Full details of the search strategy can be found in the Primary Research Appendices.

A The Impact of mBC on Patient Social Relationships

Some patients feel the need to withdraw from their social network during cancer treatment, resulting in feelings of loneliness. Alternatively, friends and family may choose to refrain from contact as they are concerned about exposing the patient to infection while their immune system is suppressed. (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016; mBC Patient and Caregiver Qualitative Research, Pfizer, 2016; Leadbeater, 2008) Social withdrawal can be a particular problem during treatment with chemotherapy, and has been attributed to treatment-adverse effects causing patients to feel unwell, inability to maintain the household or offer hospitality, or to cope with changes in body image. Isolation can also occur if an existing relationship with a partner breaks down, or for those who are single. Patients in this situation describe not wanting to burden a new partner with the demands of cancer and its treatment, concerns about changes in body image, and what the future holds. (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016)

“She was hostile, did not want to see anybody, and did not want anybody to see her. She was really beautiful... She did not want people see her like that. Bald, swollen.”

Caregiver of patient with mBC, Mexico, 2016

The general public can be intentionally and unintentionally less supportive to patients with mBC. In some low- and middle-income countries, particularly among rural populations, some respondents in two surveys reported that breast cancer should not be openly discussed. (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016; mBC General Population Survey, Pfizer, 2015) They believe that mBC is contagious and ostracize patients by avoiding or refusing to eat with them. (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016) As discussed in detail in Section 2, Chapter 3, *Public Understanding of mBC*, public understanding of mBC is limited, which has exacerbated the mBC patients' feelings of isolation and stigmatization. Some of the general public either refer to mBC in terms of an imminent death sentence, or do not differentiate between mBC and eBC and, hence, are overly optimistic. In this case, they minimize or misunderstand the seriousness of the situation by telling the patient that they are going to be fine, or that mBC can be cured (Figure 2.20). These two extremes of popular opinion regarding the severity of mBC leave patients either

Some of the general public either refer to mBC in terms of an imminent death sentence, or do not differentiate between mBC and eBC and, hence, are overly optimistic.

(mBC Patient and Caregiver Qualitative Research, Pfizer, 2016)



“I have other friends that said, ‘You’re going to be fine,’ and I wanted to punch them. I thought, I’m not fine.”

Patient with mBC, US

despairing, with a diminished sense of hope, or frustrated and inhibited to share their own fears. Furthermore, mBC patients highlighted examples of media campaigns in the UK and US that give a sense that they are to blame for their diagnosis by drinking alcohol, smoking, or not having children. Fundraising or awareness building efforts such as “no bra day” are considered by mBC patients to be insensitive, particularly to those who have had their breasts removed after breast cancer surgery. (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016)

Figure 2.20

The Challenges of Extreme Societal Opinions Regarding mBC

mBC Patient and Caregiver Qualitative Research, Pfizer, 2016

| mBC Attitudes | |
|--|--|
| <i>Death sentence</i> | <i>Curable</i> |
| Some believe people with mBC will die very soon | Others are overly positive, thinking people can “beat” mBC |
| Driven by perception that all cancer is terrible / imminently fatal | Typically driven by visibility of success stories in eBC |
| Or by perception that once cancer spreads, end-of-life must be close | Patients themselves may believe their mBC can be cured – in some cases, the medical team appears to have painted an overly positive picture |

As a result of these experiences, patients ignore or reduce contact with those in the general public that they find less supportive or understanding. (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016) However, respondents recognize that their close network of supporters remain there for them, despite the challenges of their diagnosis. In fact, experiences with their social network are on the whole positive. Interpersonal relationships frequently become stronger, with the support group becoming very protective of the person with mBC. (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016)

Patients ignore or reduce contact with those in the general public that they find less supportive or understanding.
(mBC Patient and Caregiver Qualitative Research, Pfizer, 2016)

Spouses, friends, and family, play a critical role as a support network for those diagnosed with mBC. In the mBC Patient and Caregiver research, a ranking of primary concerns illustrates the breadth of fundamental issues with which mBC patients struggle (Figure 2.21). (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016) Those with mBC describe friends, family, and their spouse or partner, as their best source of support and help with coping. (Hasson-Ohayson, 2010; mBC Patient and Caregiver Qualitative Research, Pfizer, 2016) However, at an individual level, the network of support can be much broader than this and could include, medical staff, neighbors, local store owners and, of course, other people receiving similar treatment either met face-to-face or through social media. (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016) Those who are religiously engaged, find the ongoing support of their clergy or congregation has a positive effect on their mood. Maintaining spiritual support by meeting



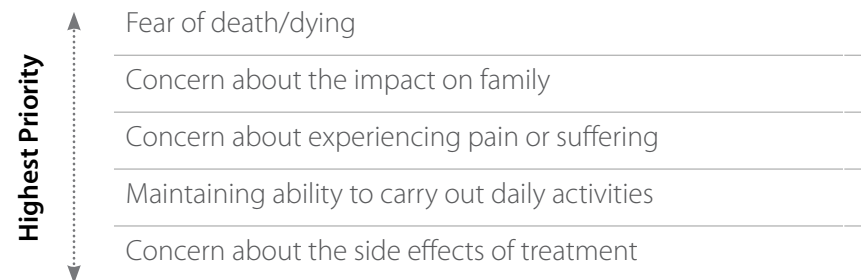
Those with mBC describe friends, family, and their spouse or partner as their best source of support and help with coping. (Hasson-Ohayson, 2010; mBC Patient and Caregiver Qualitative Research, Pfizer, 2016)

individual preferences for a faith leader or congregation contact, either at home or through assisted visits to the patient's place of worship, is associated with decreased depression during periods of serious ill health. (Hays, 2011)

Figure 2.21

Primary Patient Concerns

mBC Patient and Caregiver Qualitative Research, Pfizer, 2016



Ultimately, any member of the support network may be the caregiver, but frequently this function is performed by the patient's spouse or children. (Feiten, 2013) The presence of a caregiver is important for the patient's feeling of social support. Women with mBC who had a caregiver were more likely to feel satisfied with the social support that they received from friends and family, compared with those women who did not. (Mertz, 2013)

The care needs of patients evolve over time, increasing as the consequences of mBC and its treatment limit physical abilities. (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016) Support is required in practical, financial, and emotional ways. Patients describe how their supporters attend doctor or treatment appointments with them, provide personal care such as washing and feeding, are there to talk when they need them, and will comfort them when they feel emotional. Other practical acts of support include child care, cooking, cleaning, taking patients out, or running errands. (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016) However, patients describe that the most helpful support they receive from caregivers is emotional. It boosts their morale, helps them to stay positive but realistic, keep strong, and doesn't deny their struggles but allows them to express the emotions that they are feeling. In many situations, caregivers will also provide financial support by paying for treatment and hospital visits. (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016)

“Then, my biggest worry was finding a way of telling my mother, who has a heart condition, and telling my children. I thought about them. I never thought: ‘I’m going to die.’ Frankly, I never thought about that. I thought: My God, how can I look after my family now? ”

Patient with mBC, Brazil, 2016



“They supported me in terms of everything.”

Patient with mBC, Egypt, 2016

In some countries, the patient is protected by caregivers from the realities of an mBC diagnosis. (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016) The mBC Patient and Caregiver Qualitative Research identified examples in some low- and middle-income countries, where patients are “protected” from their mBC diagnosis by their caregivers and doctors. (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016) The reasons for this are sociocultural and reflect the contrast between a Western approach to informed consent and patient autonomy, and a family-centered approach to decision-making, which is still prevalent in some countries. (Aljubran, 2010; Chittem, 2015) Members of the family may request non-disclosure of mBC diagnosis due to the perception of hopelessness and concerns about the psychological impact on the patient. Some family members believe that patients, especially older women, would become overwhelmed by the bad news or weight of decision-making and, hence, these family members take over responsibility for this. (Aljubran, 2010)

“We told her that she has a herniated disk, but that she can’t undergo surgery due to the presence of a tumor... [Family and friends] are not allowed to talk to her about it. I told them all to not mention the disease to her at all.”

Caregiver of patient with mBC, Egypt, 2016

While patients in family-centered cultures accept that their family will take over some or all of their responsibilities, in other cultures, patients feel ambivalent or find it difficult to accept offers of help for a number of reasons. They want to maintain their identity for as long as possible and are concerned about the financial, emotional and practical burdens arising from prolonged treatment for mBC. Patients may also feel responsible for the disruption that their illness has caused to the lives of those close to them and, hence put on a brave face to protect their loved-ones as much as possible from the situation. (Sulik, 2007; mBC Patient and Caregiver Qualitative Research, Pfizer, 2016) In certain circumstances, patients with mBC might try to protect some members of their support network, especially close family, who find the situation difficult to handle. This can create a feeling of distance in the relationship as information about the disease and treatment is passed on, only on a “need to know basis.” (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016)

In certain circumstances, patients with mBC might try to protect some members of their support network, especially close family, who find the situation difficult to handle.

(mBC Patient and Caregiver Qualitative Research, Pfizer, 2016)



B The Impact of mBC on Caregiver

The responsibility of caregiving for someone with mBC has a significant effect on the caregiver. In a 2015 public survey, respondents from the general public across 14 countries recognized that mBC puts a considerable emotional strain on family and friends. (mBC General Population Survey, Pfizer, 2015) Family caregiving for patients with end-stage medical conditions is potentially life changing. (Hasson-Ohayson, 2014) Caregiver's worries focus on their loved one's well-being, disease status, and ability to maintain life activities. (Mayer, 2015) Feelings about the situation are complicated, and caregivers may find the role can be positive, but also stressful. (Badr, Health Psychol, 2010) They describe the experience as both profound and overwhelming, and perceive any burden associated with caring increases as the functional status of their loved one declines. (Hasson-Ohayson, 2014; Mayer, 2015; Grunfeld, 2004) Some do feel unappreciated. (Mayer, 2015) However, in a survey of mBC caregivers in the US, while 50% felt that no one understood what he or she was going through, the majority agreed that they always try to maintain a positive outlook and many feel that their caregiving is a choice, not an obligation. (Mayer, 2015)

In a survey of mBC caregivers in the US, while 50% felt that no one understood what he or she was going through, the majority agreed that they always try to maintain a positive outlook and many feel that their caregiving is a choice, not an obligation. (Mayer, 2015)

A Canadian survey of 89 caregivers of patients with mBC found that approximately two-thirds reported some form of adverse impact on work.

(Grunfeld, 2004)

The literature search found research on the effects of caregiving on spouses. A diagnosis of mBC affects both members of a couple, and the patient and his/her partner often acts as a primary source of support for each other. (Badr, Health Psychol, 2010) The demands of providing care for a loved one extends beyond personal relationships; caregivers experience psychological and economic strain resulting in decreased well-being and symptoms of stress. (Grunfeld, 2004; Hasson-Ohayson, 2010; Hasson-Ohayson, 2014) Notably, the economic burden to caregivers is often overlooked and poorly understood. (Wan, 2013) A Canadian survey of 89 caregivers of patients with mBC found that approximately two-thirds reported some form of adverse impact on work. This included work-absence or the need to take annual or special leave as a result of caregiving responsibilities. In a small number of cases, caregivers had to give up work or decline opportunities for promotion. (Grunfeld, 2004)



“It’s different. [Her husband] kind of distances himself a bit, like he wants to break down and cry and he’ll go out and drive, but he can’t handle it as much. He doesn’t know much detail about what’s going on because she knows he can’t really handle it so it’s distant in terms of that.”

Caregiver of patient with mBC, US, 2016

When the caregiver is the spouse, the demands of caregiving can also result in marital strain. (CBCN, 2010) Emotional distance can be created as couples cope with cancer; potentially contributing to impairment in sexual relationships and decreased marital satisfaction. (Milbury 2013) Spouses of patients with breast cancer are known to be directly affected by the illness, with the impact being greatest in spouses of those with mBC. (Hasson-Ohayson, 2010; Badr, Health Psychol, 2010) Although the evidence is not clear-cut, some studies found that the distress experienced by spouses may be greater than that of the patient with mBC themselves. (Hasson-Ohayson, 2010) In fact, levels of anxiety and depression were higher in caregivers than patients during the terminal phase of mBC. (Grunfeld, 2004) Caregiver’s stress and the demands of caring may impair their ability to provide adequate support for their loved one, (Badr, Health Psychol, 2010) and can manifest as caregiver ill-health through the abandonment of his or her own self-care needs. (Blum, 2010)

Age and gender are relevant variables in the experiences of caregivers. In general, spouses report significantly lower levels of social support from friends and family. Younger spouses appear to experience greater distress than older spouses perhaps because of the need to juggle work and child care commitments resulting in feelings of being overwhelmed. (Hassan-Ohayson, 2010; Hassan-Ohayson, 2014) Furthermore, evidence suggests that this strain may be greater for men than women. Men, who are traditionally thought of as relying solely on their spouse for emotional support, might undergo a period of readjustment as they need to find another source of

such support. (Hasson-Ohayson, 2010) This readjustment can be challenging to the partner with mBC, and they may feel upset by the fact that they are no longer able to fulfill their responsibilities to their spouse. (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016)

Caregiver’s stress and the demands of caring may impair their ability to provide adequate support for their loved one and can manifest as caregiver ill-health through the abandonment of his or her own self-care needs.

(Badr, Health Psychol, 2010; Blum, 2010)

Addressing the needs of caregivers, particularly spouses, is important but not often considered. Just as mBC patients need practical, emotional and financial support, so do caregivers. However, their support needs are often overlooked. Spousal distress may go unnoticed when spouses are seen as caregivers, not as individuals in need of care themselves. (Hasson-Ohayson, 2010) In fact, patients with breast cancer remain a significant source of support to their spouse despite having increased support needs of their own. Caregiver support networks are important in mitigating the distress caused by the disease to both patient and caregiver. The support from friends and family appears to provide



greater protection from psychological distress than the support the spousal partnership offers. (Hasson-Ohayson, 2010) Importantly, the beneficial impact of a social support system appears consistent over all stages of the disease. The support given to the spouse is of equal importance as the support given directly to the patient in determining the patient's level of distress. Spousal support provides a buffer against both the emergence of depression and anxiety amongst patients with mBC, and the psychological wellbeing of both the patient and spouse. (Hasson-Ohayson, 2010) It has been suggested that this is because, in the case of a female patient, spousal support allows her to relinquish her normative role as a care provider to her husband at a time when she needs to focus on her own wants and needs. (Hasson-Ohayson, 2010) This suggests a need for couple-focused interventions to ensure that both members of the couple can adaptively cope with cancer together. (Badr, Health Psychol, 2010)

In conclusion, primary research showed that patients with mBC may actively reduce the size of social networks to those who matter to them the most. In this regard, patients, on the whole, feel well supported by their spouse, family and friends. The support needs of caregivers are currently largely unmet. Caregivers described wanting access to support services or support groups but were unable to find such support at the time of their loved one's diagnosis. (Mayer, 2015) It is important to recognize that preferences for support vary with the age of the caregiver. While older spouses tend to look to the family for help, younger spouses are more likely to look to their friends. (Hasson-Ohayson, 2014) Strategies are needed to identify and meet the psychosocial, occupational and financial needs of caregivers given the challenges of balancing work, commitments at home and caregiving. (Grunfeld, 2004) Resources and sources of support are also required for family members and other members of the support network. (Mertz, 2013)



Angela Barker, mBC patient from the UK, with her daughter, Sarah-Jane. Angela was diagnosed in February 2016 and is living with mBC.



Emerging Recommendations

This section discussed a broad scope of political, societal and community factors that impact mBC patient care. Although insight has been shared broadly around policy approaches and the economic burden associated with mBC, recommendations largely focus on continuing to educate and inform relevant stakeholders on the role of policy in mBC care and the economic impact of the disease. While negative perception and misunderstanding around mBC exists globally, approaches and strategies to address this will vary depending on each country and its resources. There are opportunities to drive change through improved education and awareness across both the general public and Patient Support Organizations (PSOs), which are discussed in the recommendations below.

Ultimately, the following recommendations will need to be solidified through further dialogue and will require long-term commitment across a broad range of stakeholders to see effective change for mBC patients across the world.

Broaden the approach to health policy development beyond screening and early detection of breast cancer

- Identify the elements of effective health policy that will positively influence mBC care
 - Emphasize that while screening and detection of eBC is important, it will not address the needs of those who are diagnosed with mBC
- Address inherent limitations in healthcare systems to improve outcomes for patients with mBC
- Accurately quantify the burden of mBC within a population to allow policy makers to make informed decisions about the needs of their communities
- Capture and promote the experience and needs of patients with mBC to national level health planners and policy makers

Increase understanding and awareness of the costs of mBC, from an individual perspective as well as from a health system or societal perspective

- Recognize the excess financial impact and associated distress of mBC on patients and their families/caregivers, particularly at the end-of-life, compared to eBC
- Openly discuss costs of treatment options and potential reduced work productivity so patients are able to make appropriate financial plans for the future, this may be particularly impactful to younger patients
- Create financial support services that can help patients manage the acute financial difficulties many describe experiencing during mBC treatment

Investment in education campaigns and outreach strategies is needed to grow awareness and action around mBC, in the same way that has been done for eBC

- It is necessary to educate not only patients, caregivers and healthcare professionals, but philanthropists, government officials, general public journalists, and other key stakeholders, in order to harness a successful advocacy movement
- Emphasize with PSOs specifically the great need for long-term and often increasing assistance for mBC patients
- In limited-resource countries, appropriate advocacy and education should focus government attention on the growing burden of breast cancer, including the untimely deaths due to mBC, and highlight the need for increasing national focus



Increase global access and availability of PSO support services specific to mBC

- Further development of mBC-specific support services that address patient and family needs is critical, especially for younger women. These services could include peer-support networks, educational initiatives and financial support
- Increase proactive communication highlighting specific support services, including counseling and online support groups
- Enable the creation of financial support services and encourage appropriate financial planning
- Increase global accessibility to support services for all patients with mBC

Development of a globally impactful alliance for mBC advocacy, replicating some of the successes seen by organizations such as the US mBC Alliance, which include policy efforts, patient and physician communications resources and disease awareness initiatives

- Provide a platform for advocates to educate one another on how to use stories, messages, the media, and social media to transform their society's understanding of mBC
- Collectively drive the need for access to treatments and palliative care, and for research on mBC
- Develop a brief for PSOs to drive consistency of communication about mBC

Advance widespread global awareness of mBC, with honest and accurate presentation of the realistic experience of patients, enabling the wider community to better support both patients and their caregivers in managing the impact of mBC on their lives

- Encourage public figures with mBC to share their experiences, similar to that which has been seen for eBC
- Provide mBC with a distinct identity separate from eBC
 - Globally leverage Metastatic Breast Cancer Awareness Day beyond the current reach to expand this initiative across more countries and with increased visibility

Empower media (both traditional and social) to deliver tailored, evidence-based approaches to mBC communication and education

- Engage key global experts to directly educate the media about mBC care globally and the need to drive change
- Utilize traditional media to guide the general public to appropriate sources of mBC information
- Develop a reporting brief for the media regarding best practices in reporting mBC and advanced cancer generally



Better attention should be given to the needs of patients with mBC in the workplace

- Exploration of employment rights in each country to determine how these currently meet the needs of employees with mBC and what changes are required to facilitate a return to work after a diagnosis of mBC
- Greater access to financial support for those without an employer or in self-employment
- Development of educational materials to create greater understanding among employers and primary care/occupational health staff about the pressures of an mBC diagnosis on working life
- Guidance for employers that support employees with mBC in their desire to return to work and where, particularly, their ability has been compromised

The societal impact of mBC on patients with the disease and their caregivers needs to be understood

- Greater public understanding of a diagnosis of mBC is required to protect mBC patients from the need to withdraw from social networks that share extreme perceptions that the disease is an imminent death sentence or conversely that the patient will “just be fine”
- Greater recognition of the impact of mBC on caregivers
- A change in perspective on caregivers by health care professionals to recognize and address their care needs in a way that reflects age and gender preferences for support
- Educational materials specifically targeted at caregivers, which aims to bring them up to speed on the matters of greatest importance that informs the medical care of their loved one and treatment options
- Provide resources to services that can support caregivers practically, financially and emotionally



Section 3

Scientific Landscape



Introduction

The global burden of breast cancer and the significant mortality that stems from metastatic breast cancer (mBC) continues to exact a toll on patients and physicians, despite the initial groundbreaking innovations in the 1990s and early 2000s that resulted in advances in knowledge, technology, and treatment. The main scientific landmarks during that time included classification of breast cancer into 3 main subtypes and introduction of endocrine therapy for hormone receptor-positive (HR+) disease and targeted therapy for human epidermal growth factor receptor 2 positive (HER2+) disease. Advances in innovation and attendant outcomes have been less sizable in the last decade. Complicating the translation of knowledge into new therapies is the evidence that breast cancer is much more heterogeneous than previously understood, with the existence of additional subtypes within the 3 main subtypes that have traditionally informed treatment decisions. However, despite the challenges to date, opportunities abound to create meaningful change for individuals with mBC through the convergence of diverse, yet interrelated scientific approaches, including advances in understanding the molecular basis of mBC; improved clinical trial designs and endpoints to support a robust pipeline that could yield novel therapies, combinations, and sequences; and more.

To better understand where mBC has been and where it will go, this chapter captures an overview of the scientific progress in mBC over the past 10 years, acknowledges the groundbreaking advances that occurred more than 10 years ago, and focuses on future advances.

Methodology: Secondary research and analyses were conducted to evaluate scientific progress in mBC across different dimensions. This included evaluation of progress in mBC relative to the progress observed in early breast cancer (eBC), assessment of the differences in progress

in mBC according to the 3 main subtypes, and examination of whether progress in mBC has kept pace with progress made in the treatment of other metastatic cancers. Because of the wide-ranging ground covered, a multitude of factors were considered in the analysis and included changes in outcomes, advances in disease understanding, introduction of new treatments, etc. Highlights of ongoing scientific work that are likely to impact the care of mBC patients in the future were captured as well. Timing and methodology for all information provided appears throughout the report and in the appendices.

The themes examined form the chapters of this section:

- **Global Burden of Breast Cancer**
- **History of Progress in Breast Cancer**
- **mBC Innovation Plateau**
- **Focus for the Future**

The field of oncology is broad and evolving, and it is beyond the scope of this report to capture all advances in mBC. Food and Drug Administration (FDA) approvals and clinical data in mBC are through 2014 and do not reflect new data and approvals in 2015. As such, the Focus for the Future section embodies emerging recommendations that require a broader dialogue within the scientific community.

Additionally, despite the focus on mBC, the importance of continued innovation in eBC must also be emphasized because of its key role in improving cure rates and thereby decreasing the proportion of patients who may eventually develop mBC.



Chapter 1: Global Burden of Breast Cancer

- Breast cancer represents a significant public health burden across the globe with increasing incidence rates. Mortality rates, predominantly due to mBC, have remained stable at best but the absolute number of deaths is rising
 - Wide variations exist in country-specific trends
 - From some clinical learnings, approximately 20%-30% of eBC patients may recur with mBC

A Breast cancer represents a significant public health burden across the globe

Breast cancer is the most common cancer in women with an estimated 1.7 million new cases diagnosed in 2012 worldwide. (IARC, Breast Cancer, 2015; Lu, 2009) While great progress has been made in the management of breast cancer, it remains a significant global health issue. (IARC, Breast Cancer, 2015) Between 2008 and 2012, for example, breast cancer incidence (rate of new breast cancer cases) increased while mortality (death rate) remained relatively stable based on Global Burden of Cancer Study (GLOBOCAN) data from more than 180 countries. (Ferlay, 2010; Ferlay, 2015) However, as country-specific trends vary widely and may differ from global trends, it should be recognized that there are wide variations in both incidence and mortality rates, depending on the quality of the data reported and the country examined (Figure 3.1). (Ferlay, 2015; DeSantis, 2015) It has been reported that breast cancer incidence and mortality rates have stabilized or decreased in high-income countries between 1993 and 2012, whereas, the incidence and mortality rates have increased in developing countries—partly due to lifestyle changes and a lack of access to early detection, diagnosis, and treatment—between 1993 and through 2012. (DeSantis, 2015; IARC, Breast Cancer, 2015)

*Based on data from more than 180 countries. (Ferlay, 2010; Ferlay, 2015)

†Long-term data series from cancer registries and the World Health Organization mortality database were used to assess trends in incidence in 39 countries and trends in mortality in 56 countries from 1993 up through 2012. (DeSantis, 2015)

- Breast cancer is a heterogeneous disease that cannot be approached or treated in a one-size-fits-all fashion
 - Estrogen receptor-positive (ER+) breast cancer will continue to be the largest breast cancer subtype
 - Clinical outcomes for HER2+ breast cancer, once considered poor, have greatly improved in recent years
 - Triple negative breast cancer (TNBC) is the most aggressive subtype, leading to a higher proportion of overall breast cancer mortality than other subtypes

Figure 3.1

Trends in Breast Cancer Incidence and Mortality Rates

Ferlay, 2010; Ferlay, 2015; DeSantis, 2015

| | ▲ Increasing | ▼ Decreasing | ◀▶ Stable | Incidence | Mortality |
|---|--------------|--------------|-----------|-----------|-----------|
| GLOBOCAN 2008 through 2012* | | | | ▲ | ◀▶ |
| Incidence: 39.0 to 43.3 | | | | | |
| Mortality: 12.5 to 12.9 | | | | | |
| Select country-specific trends, 1993 through 2012† | | | | | |
| Colombia, Ecuador, Mexico, Japan | ▲ | | | ▲ | ▲ |
| China | ▲ | | | ▲ | ◀▶ |
| Costa Rica, Czech Republic, Denmark, Finland, Iceland, Germany | ▲ | ▼ | | ▲ | ▼ |
| Brazil | | | ◀▶ | ◀▶ | ▲ |
| Australia, Canada, United Kingdom, United States, France, Switzerland, Spain, Italy | | ▼ | ◀▶ | ◀▶ | ▼ |
| Singapore | | ▼ | | ▼ | ◀▶ |
| Israel | | ▼ | | ▼ | ▼ |



Yet despite the decline in some rates, the absolute number of deaths from breast cancer globally is still high and increasing. (WHO, 2013) In the US, the number of deaths has remained constant at approximately 40,000 deaths per year over the last 30 years. (NCI SEER, 2015; ACS, 2003; Dawson 1989)

There were an estimated 561,334 deaths worldwide in 2015 and an estimated 805,116 by 2030, representing a 43% increase in absolute number of deaths from breast cancer. (WHO, 2013)

It is important to remember that the majority of these deaths are due to metastatic disease and even in developed countries the burden remains significant. (Lu, 2009; DeSantis, 2015; IARC, Breast Cancer, 2015) Although country-specific figures vary widely and may reflect national economic status, published data suggest that, globally, 5%-10% of newly diagnosed breast cancer patients will present with metastatic disease. (Cardoso, 2012) Overall, in high-income countries, less than 8% of breast cancer patients are initially diagnosed with advanced disease compared with 50%-80% in the majority of low- and middle-income countries. (Unger-Saldana, 2014) In developed countries, clinical studies have shown that approximately 20%-30% of women diagnosed with eBC may progress to mBC, and this number may be higher in less developed countries where treatment standards for eBC may be less advanced. (O'Shaughnessy, 2005; EBCTGG, 2015)

B Breast cancer is a heterogeneous disease that cannot be approached or treated in a one-size-fits-all fashion

Breast cancer can be categorized into 3 main subtypes based on the expression of diverse receptors, some of which are normally expressed in human cells (ie, estrogen and progesterone receptors; Figure 3.2).

(Howlader, 2014; ACS BC, 2015) These receptors act as biomarkers and are both prognostic (indicating the likely course of the disease) and predictive of response to targeted therapies. (Santa-Maria, 2015)

Broadly, breast cancer is categorized as:

- **Hormone receptor-positive (HR+):** Presence of either estrogen (ER+) and/or progesterone receptors (PR+). (ACS BC, 2015) This is the largest subtype of breast cancer, with approximately 60% of breast cancers being HR+. (Howlader, 2014) It is sometimes also referred to as luminal A and luminal B subtypes in the literature (ER or PR positive and Ki-67 index $\leq 14\%$ or ER or PR positive and Ki-67 index $> 14\%$, respectively). (Bonotto, 2014) The hormone receptor remains the most validated target in breast cancer, and the first systemic therapies for breast cancer were endocrine therapies for the HR+ subtype in mBC. (ASCO BC, 2015; Santa-Maria, 2015) Their introduction changed the treatment paradigm and these treatments continue to be relevant in eBC and for patients who have progressed to mBC. (ASCO BC, 2015; NCCN Guidelines® for Breast Cancer V.3.2015, 2015) Despite the change in the treatment paradigm, new unmet needs have arisen, such as treatment of individuals who progress or who develop resistance. (Yamamoto-Ibusuki, 2015; Santa-Maria, 2015)
- **Human epidermal growth factor receptor-2-positive (HER2+):** Presence of HER2 receptor. (ACS BC, 2015) Discovery of the HER2 mutation as cancer-causing was an important breakthrough leading to significant advances in the treatment of HER2+ breast cancer, which have continued over the past several years. (Santa-Maria, 2015; Zelnak, 2015) As a result, there are now multiple therapies in the treatment repertoire targeting HER2 and clinical outcomes for this breast cancer subtype, once considered poor, have greatly improved. HER2-targeted therapy in mBC has also been associated with the development of resistance. (Zelnak, 2015, Santa-Maria, 2015)



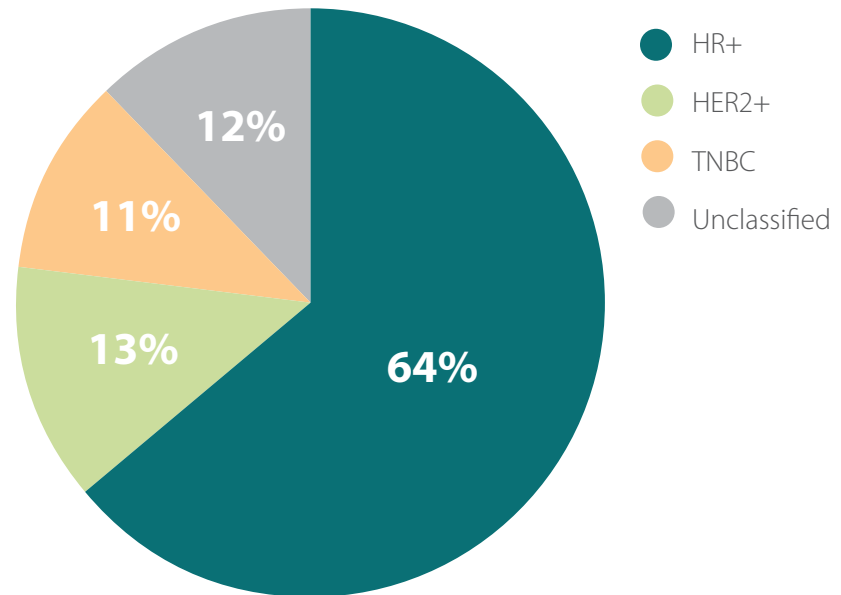
• **Triple-negative breast cancer (TNBC):** Heterogeneous group of tumors more recently categorized as a subtype of their own that does not express either PR, ER, or HER2. (Clarke, 2012; Allison, 2012; Lehmann, 2011) Although TNBC only represents <15% of total cases of breast cancer in developed regions compared with a larger proportion in developing regions, it is the most aggressive subtype and the proportion of overall breast cancer mortality due to TNBC is much higher than other subtypes. (Howlader, 2014; Huo, 2009) TNBC diagnosis is challenging because current treatment options are limited to cytotoxic agents, which have limited efficacy. (Santa-Maria, 2015) As TNBC is a diagnosis of exclusion (eg, patients who are not positive for ER, PR, or HER2), future subtype differentiation should hopefully help to define the patients in this population and afford them new targeted treatment options.

It is important to note that research studies do not consistently report the receptor subtypes investigated and to recognize that outcomes vary based on the full receptor expression profile (eg, HR+/HER2- vs HR+/HER2+). (Bonotto, 2014) Receptor subtype data included in this document are as presented in the original studies and are broadly comparable, although variations may exist.

Figure 3.2

Subtype Distribution Based on US Surveillance, Epidemiology, and End Results (SEER) Registry Data

Howlader, 2014



Chapter 2: History of Progress in Breast Cancer

- Over a decade ago, innovations in breast cancer resulted in notable progress in treatment. These innovations were built on a foundation of gains in understanding the biology of the disease, risk stratification, subtyping, and development of the first targeted treatments
 - eBC has benefited the most from this progress. Screening for early detection and treatment have contributed to a decrease in recurrence rates and progression to mBC. Innovations in these areas are credited with much of the decline in breast cancer mortality, particularly in developed countries
 - Paradigm-changing historical advances in mBC management include the introduction of aromatase inhibitors (AIs) for ER+ mBC in 1996 and HER2-targeted therapy in 1998
- In the past decade, progress in the management of breast cancer has continued, but the advances in mBC have been incremental compared to the previous decades
 - There have been modest improvements in outcomes in mBC
 - Innovation has not been comparable across all mBC subtypes, with greater success occurring in HER2+ mBC
 - Progress made in the scientific understanding of mBC has highlighted the previously unrecognized complexity of the disease

A Significant innovations occurred in breast cancer over a decade ago

Most major innovations in breast cancer date back more than a decade and encompass a wide array of advances beyond treatment. (ASCO BC, 2015) The foundations of early therapeutic progress relied upon an increased understanding of the biology of disease, discovery of different breast cancer subtypes with associated variations in outcomes, identification of risk markers, and improvements in screening. (ASCO BC, 2015) In particular, the increased use of mammography screening has enabled breast cancer to be detected in earlier stages, when therapies are more effective, and has been credited with much of the decrease in mortality in countries with widespread implementation. (ASCO BC, 2015) For example, high screening and early detection rates have resulted in a 27% decline in breast cancer mortality in the United States in the past 40 years,

although the overall number of deaths has stayed constant at 40,000 for the past 30 years. (ASCO BC, 2015; Dawson, 1989; NCI SEER, 2015)

The first systemic therapies developed in the 1970s and 1980s for mBC were hormone therapies: luteinizing hormone-releasing hormone agonists and endocrine therapy. (Crighton, 1989; Bernard-Marty, 2004) The 1990s saw the introduction of AIs—potent hormone therapies that block estrogen production—for HR+ mBC. (Bernard-Marty, 2004; Altundag, 2006) However, it is in HER2+ breast cancer, which represents <15% of mBC, (Howlader, 2014) that the most innovations have occurred in recent years. In 1998, the first targeted therapy, trastuzumab, widely known as Herceptin® (note: Herceptin is a registered trademark of Genentech), was introduced for HER2+ breast cancer. (Trastuzumab, 2015) This targeted therapy was approved along with a companion diagnostic to identify susceptible tumors, representing another important milestone. (Genentech,



2015) In subsequent years, additional therapies targeting HER2 have been developed, allowing clinicians to combine therapies that target the same molecular pathway. (ASCO BC, 2015) Additionally, an innovative treatment combining a HER2-targeted agent plus chemotherapy was designed to deliver the drugs directly to the tumor and help minimize damage to healthy tissue. (ASCO BC, 2015) Some of the notable advancements from the past decade are highlighted in Figure 3.3.

“ Aspects of breast cancer treatment underlie much of the observed improvement in breast cancer mortality and survival between the 1970s and 2000s. Those decades saw remarkable scientific advances, including identification of the human epidermal growth factor receptor 2-neu (HER2-neu) oncogene and development of the targeted agent trastuzumab... ”

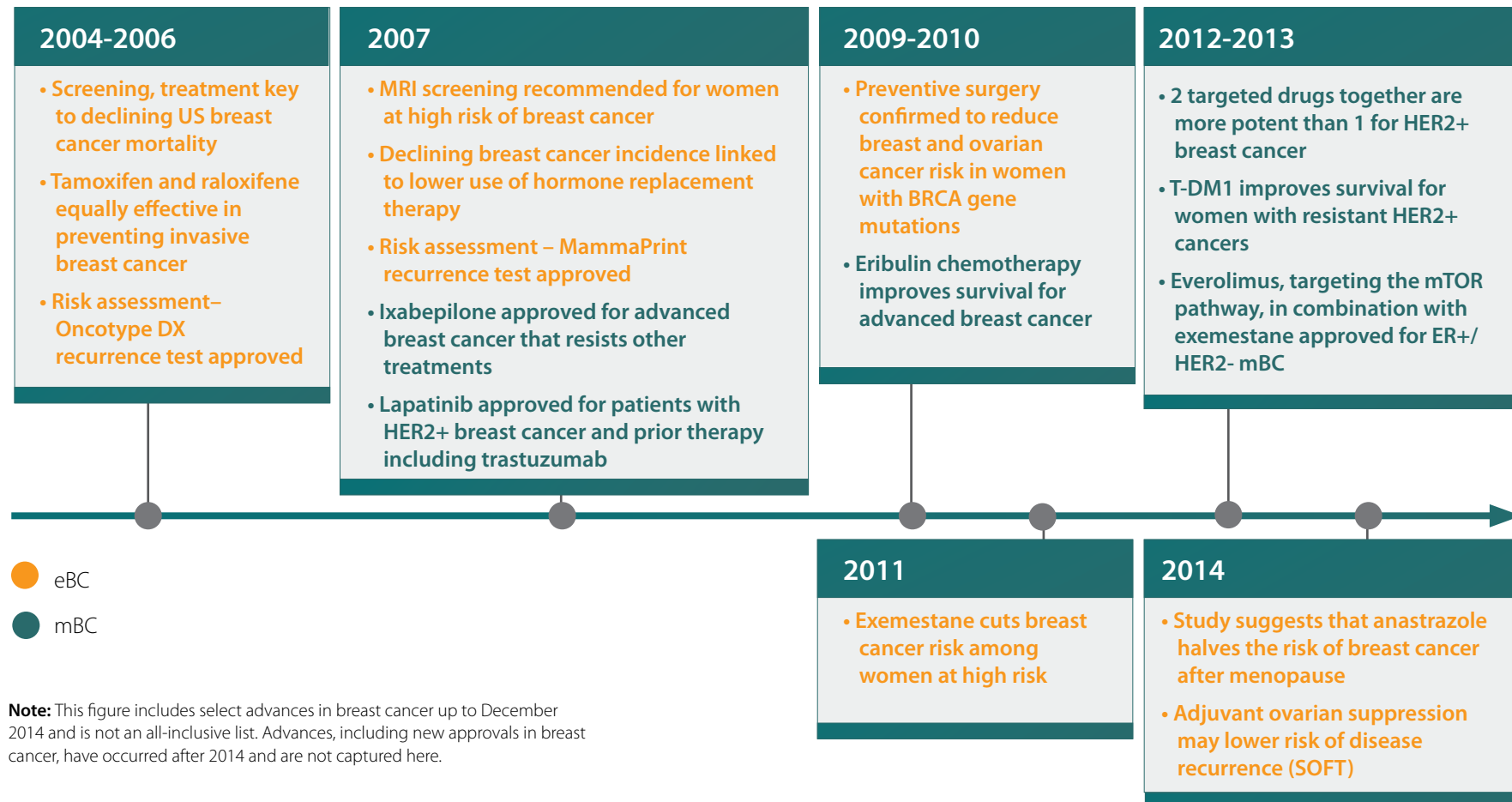
Elkin EB and Hudis CA. J Clin Oncol. 2015;33(10):2837-2838.

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Figure 3.3

Select Advances in Breast Cancer in the Past Decade Through December 2014

ASCO BC, 2015; BCA, 2015; FDA 2006-2009, 2015; Ixabepilone, 2015; NCI lapatinib, 2015; NCI bevacizumab, 2015; Masters, 2015; Francis, 2015



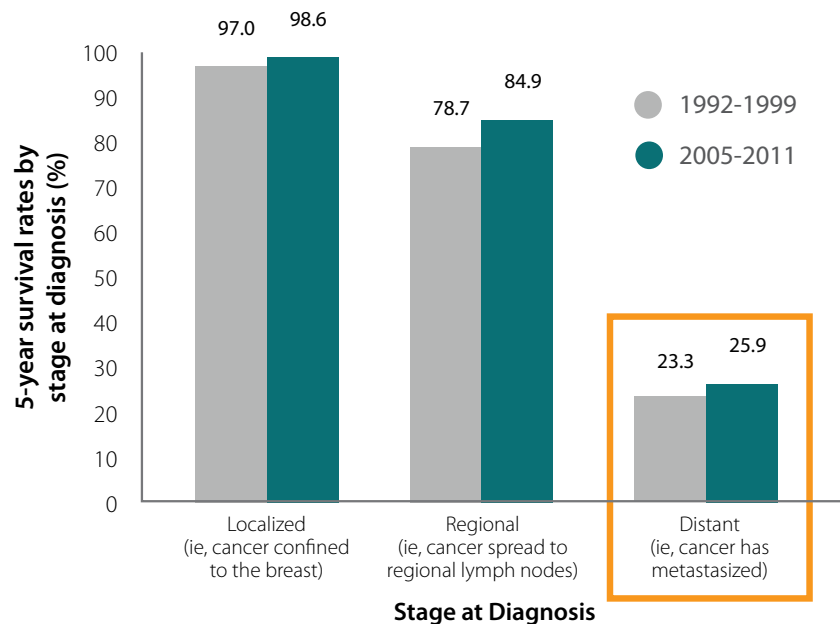
B There have been modest improvements in outcomes for patients with mBC in the past decade

Real-World Data As a result of innovations in disease understanding and treatment, high 5-year survival rates are now seen for eBC. In contrast, 5-year survival rates for mBC remain poor at approximately 25% (Figure 3.4). (ACS, 2003; NCI SEER, 2015) Based on data from developed countries gathered between 1995 and 2013, median survival for mBC is an estimated 2 to 3 years although survival varies by subtype and by patient characteristics. (NCI SEER, 2015; Weide, 2014; Lobbezoo, 2013)

Figure 3.4

5-year Survival Rates by Stage at Diagnosis (Female Breast Cancer, US SEER), 1992-1999 Compared With 2005-2011

ACS, 2003; SEER, 2015



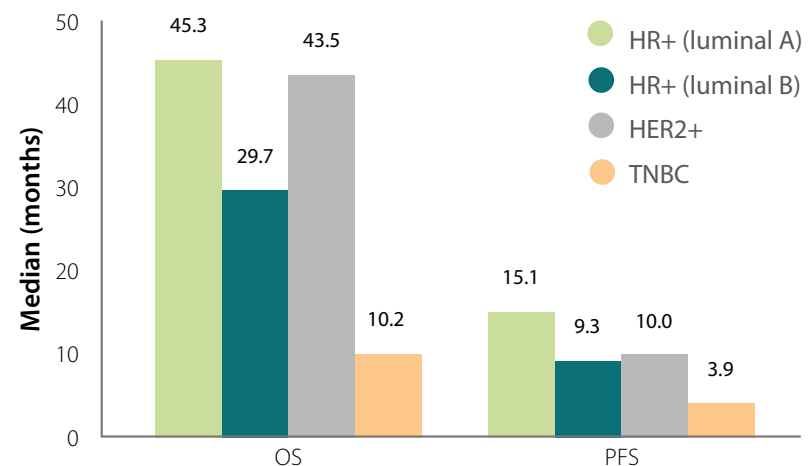
Scientific advances in the 1990s and 2000s are reflected in the improvement in outcomes in mBC during that time frame. (Albain, 2012) An 8-month improvement in median survival for mBC was observed from 1991 to 2001, corresponding with the introduction of AIs in the 90s for HR+ mBC, but subsequent progress has been limited to days/months. (Albain, 2012)

When assessing outcomes by subtype in mBC, obvious differences can be seen. Time to recurrence, location of metastatic sites, and survival times after recurrence can all vary widely. (Metzger-Filho, 2013; Tobin, 2015; Ribelles, 2013) Furthermore, whereas HR+ and HER2+ mBC demonstrate somewhat comparable outcomes, individuals with TNBC have the shortest median overall survival (OS) and progression-free survival (PFS), as illustrated in Figure 3.5. (Bonotto, 2014) These results were based on a retrospective review—conducted to analyze the impact of patient and tumor characteristics on outcomes—of 472 consecutive patients with mBC between 2004 and 2012. (Bonotto, 2014)

Figure 3.5

OS and PFS at First Line of Treatment by mBC Subtypes, 2004 to 2012

Bonotto, 2014

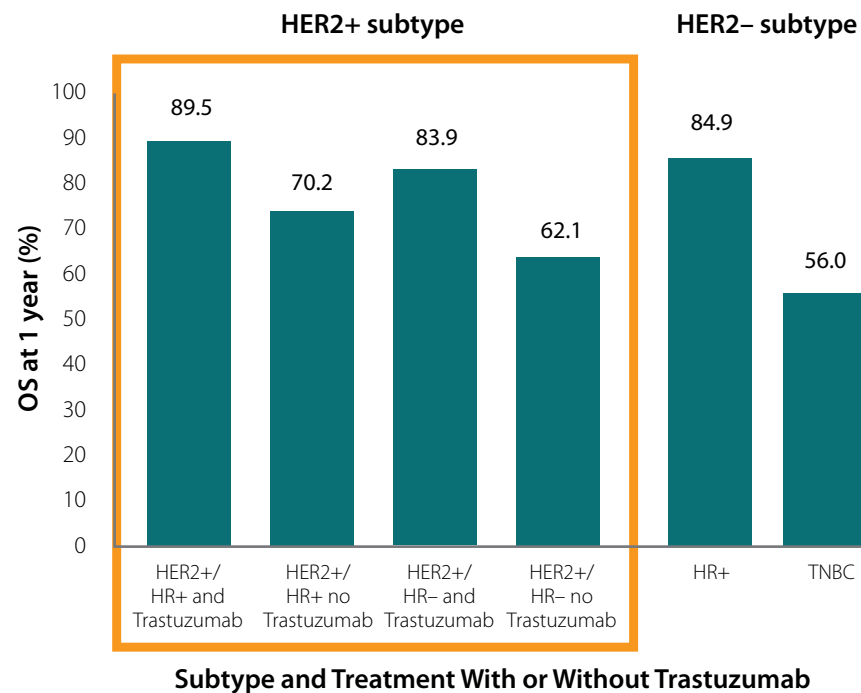


These data, while informative, highlight care provided within a specific period of time and may not fully capture the impact of more recent advances in the changing landscape of mBC treatment, particularly in the HER2+ space. The limited data available, from a study of women with mBC diagnosed between 1991 and 2007 (thereby predating approval of 3 additional HER2+ treatments), highlight the fact that innovations in mBC in the form of HER2-targeted therapy have resulted in improvements, such that HER2+ now has comparable outcomes to those seen in HR+ mBC (Figure 3.6). (Dawood, 2010; FDA 2010, 2015; FDA 2012, 2015; FDA 2015, 2015; Bonotto, 2014)

Figure 3.6

Percent OS Estimates at 1 Year by Subtype and Treatment With or Without Trastuzumab, 1991-2007

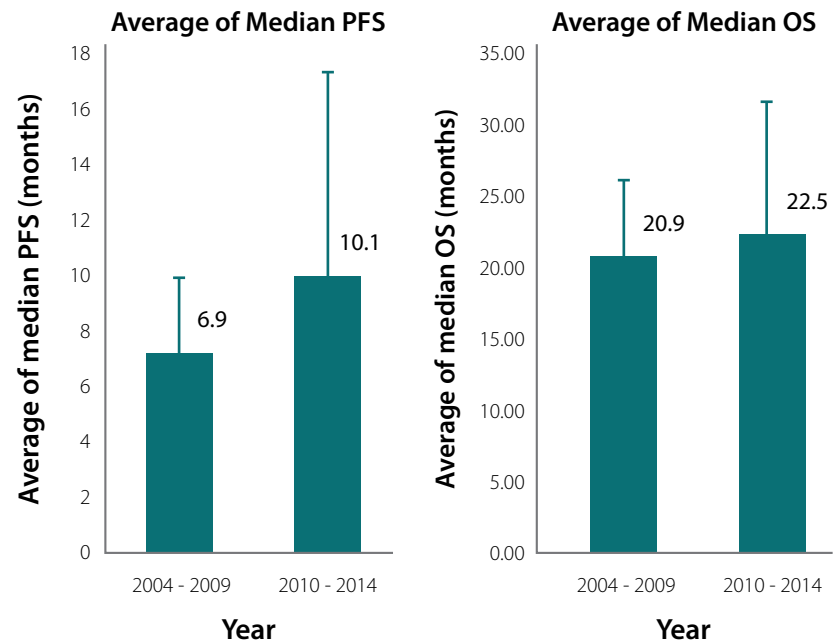
Dawood, 2010



Clinical Trial Data The relatively modest gains in survival for mBC in recent years have also been seen in the more controlled setting of Phase II and III clinical trials. A systematic literature search of Embase® (See Appendix 3.1 for search methodology) to identify all studies (clinical trials or meta-analyses) that reported median PFS or median OS was conducted. The average of the median PFS or average of the median OS was calculated for 2004 to 2009 and for 2010 to 2014, and highlighted incremental gains in outcomes for mBC (Figure 3.7). From studies conducted in the first 5 years versus the second 5 years of the past decade, there were small gains of a median of 3.2 months for PFS and 1.6 months for OS, respectively. In this analysis both interim and final PFS and OS results were included, which is a potential limitation of the analysis.

Figure 3.7

Statistically Significant Advances in the Average of the Median PFS or OS in Pivotal Phase III Registrational Studies for FDA New Approvals for the Treatment of mBC, Through 2014



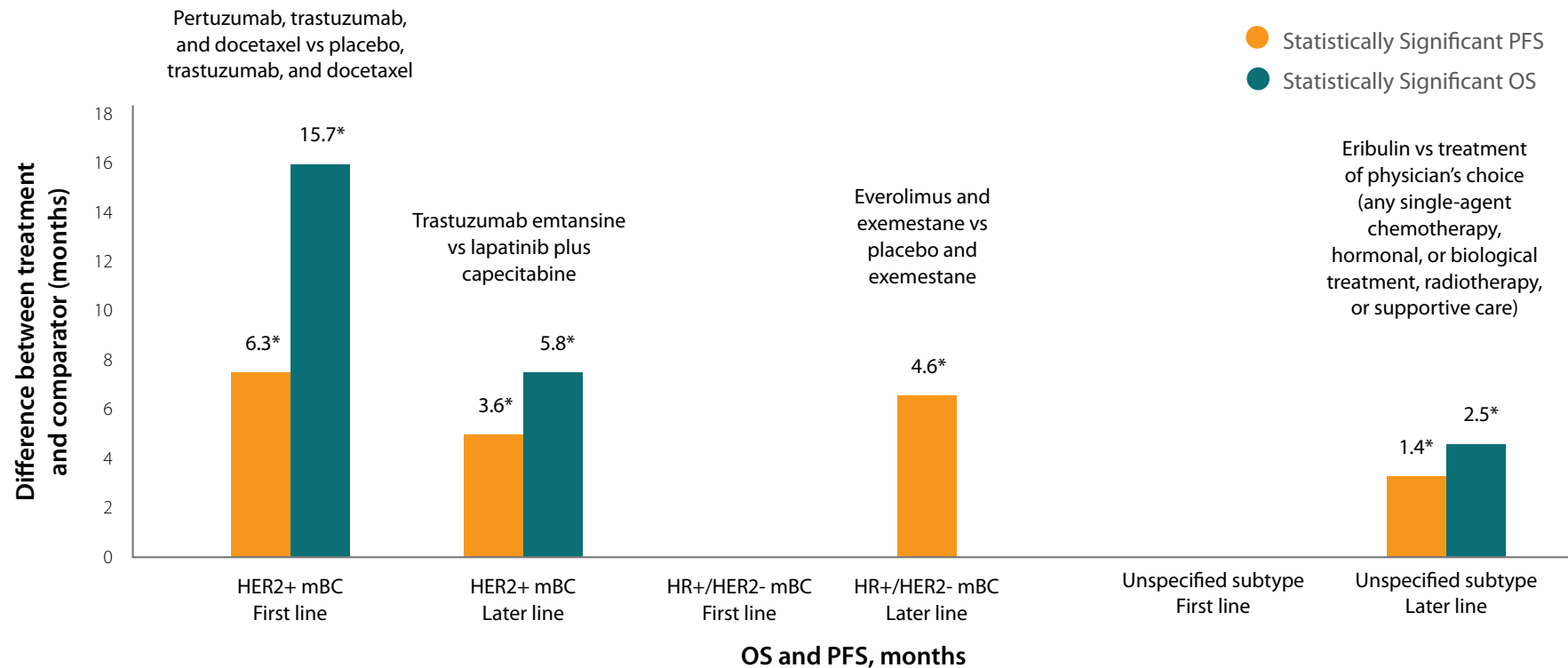
Diving deeper, improvements in mBC have not been equally demonstrated across all subtypes, particularly in TNBC, where oncologists have been most frustrated by lack of progress in increasing OS and developing breakthrough treatments. (TRM Oncology EPIC Report, 2015) Figure 3.8 below compares the changes (or improvements) in efficacy outcomes from pivotal Phase III clinical trials, as an indicator of advances in mBC by tumor subtype. For this analysis, only clinical trials that have formed the basis of new drug approvals for mBC through 2014 were included and only

statistically significant improvements were noted. These new therapies have demonstrated improved outcomes compared with the previous standards of care in the last 10 years for these subtypes. (Swain, 2015; Verma, 2012; Yardley, 2013; Piccart, 2014; Doherty, 2015) Notably, as a result of these advances, outcomes for the HER2+ subtype, once associated with a poor prognosis, have exceeded those for the HR+ subtype. (Swain, 2015; Verma, 2012; Yardley, 2013; Piccart, 2014; Doherty, 2015)

Figure 3.8

Statistically Significant Advances in Median OS and PFS in Pivotal Phase III Registrational Studies for New FDA Approvals for the Treatment of mBC in the Past Decade, Through 2014

Swain, 2015; Verma, 2012; Yardley, 2013; Piccart, 2014; Doherty, 2015



*Values represent improvement (change in PFS or OS) over control, not absolute values.

Note: Based on Phase III pivotal trials that formed the basis for approval of new treatments through December 2014. Line extensions or expanded indications within mBC added after initial approval are not included.



“ We have not been able to advance much in terms of direct benefit, but we do have an increased understanding of the ‘black box’: that there are many subtypes within this subtype [TNBC]... However, this is—by far—the subset with the least development in the past 10 years.”

Fatima Cardoso, MD, Champalimaud Clinical Cancer Centre in Lisbon, Portugal, Expert Perspectives on Current Challenges and Aspirations in mBC, TRM Oncology EPIC Report, July 2015

Despite modest improvements in outcomes, there has been progress in scientific understanding

In recent years there has been a wealth of data generated as a result of progress in scientific understanding. Tremendous strides have been made in basic research in cancer generally, as well as in breast cancer. For example, at the 2015 American Association of Cancer Research (AACR) meeting and the 2014 San Antonio Breast Cancer Symposium (SABCS), precision medicine was the focus, driven by basic research findings including:

- Greater understanding of intratumor heterogeneity, such as the existence of common mutations (aka “trunk” mutations) and offshoots of common mutations known as subclonal mutations (aka “branch” mutations) (SABCS, 2014; AACR, 2015)
- Copy number alterations may not occur over as long a period as previously believed and may occur in a short period of time (aka “punctuated burst”) (SABCS, 2014)
- Tumor invasion is not as simplistic as envisioned and involves interactions between different cancer cell clones and cancer cell populations (SABCS, 2014)
- Numerous mechanisms of resistance exist and may include reactivation of pathways, bypassing pathways, convergence of disparate mechanisms on a common process involved in development of cancer, or intrinsic resistance (BCRF AACR, 2015)
- What was thought of as acquired resistance may actually be innate resistance conferred by an extremely small number of cells (BCRF AACR, 2015)

Over the last decade, there has been increased understanding of the interrelated and underlying disparities, such as geography or ethnicity, which may contribute to some of the differences in outcomes outlined above. (IARC Breast Cancer, 2015; Huo, 2009) The International Agency on Research on Cancer (IARC) recognizes that there are huge inequalities between developed and developing countries, which manifests as differences in incidence and mortality. (IARC, Breast Cancer, 2015) Some of this may be a result of lack of access to affordable approaches to early detection, diagnosis, and treatment, thereby resulting in diagnosis at a later stage for many women; some may be due to lack of any targeted treatment for a particular subtype (ie, TNBC) which may be less prevalent in some areas of the world and more prevalent in other areas (ie, US vs African nations, respectively). (IARC, Breast Cancer, 2015; Huo, 2009)

Disparities

Dietze, 2015; Zhang, 2012; Huo, 2009; Zhang, 2006

Although TNBC appears to be less common in developed nations, in general, research has revealed that differences do exist based on other factors, such as ethnicity. Although significant advances in this subtype are still eagerly awaited, there remains a high medical need for research within TNBC. Research in the United States has found that TNBC is an aggressive breast cancer subtype with a high frequency of metastasis that disproportionately affects BRCA1 mutation carriers and women of African origin.

Additional data regarding founder populations, the small population where a mutation exists and eventually becomes prevalent in descendants of that population, can be quite telling. Specifically, the founder population of most African Americans (ie, individuals from West Africa) experience breast cancer as a virulent disease of young women. These differences compared with other populations suggest a role for environmental exposures and genetic determinants. Furthermore, in populations disproportionately affected by TNBC, early detection and treatment approaches will have a limited role given the aggressive nature of the subtype and advanced stage at diagnosis. Additional research into the etiology and pathogenesis of TNBC is needed to close the gaps and global disparities in metastatic TNBC across populations.



Chapter 3: mBC Innovation Plateau

- The pace of innovation in mBC appears to have slowed in recent years in clinical research, publications, guideline development, and treatment advances
 - HER2+ treatment continues to build off of the initial groundbreaking treatment advance from more than a decade ago, with continued improvements in treatment advances for this subtype, followed by modest improvements in HR+, and little to none in TNBC
- Innovation in mBC appears to be lagging behind that of several other tumor types, such as melanoma and lung cancer, in the last decade and particularly in the last 5 years
 - The approval of new targeted treatments in mBC has been surpassed by the approval of new targeted treatments for melanoma or lung cancer
 - Advances in the understanding of melanoma and lung cancer have identified clinically relevant subtypes, whereas treatment in mBC is still guided by previously identified subtypes HR+, HER2+, and TNBC
 - Increased knowledge of melanoma and lung cancer has been effectively translated into precision medicine and immunotherapy

A The pace of innovation in mBC has slowed down

After the initial flurry of activity observed in the 1990s with the introduction of AIs for HR+ mBC and the first personalized medicine in oncology for HER2+ mBC, the pace of innovation in mBC appears to have slowed in recent years in terms of treatment advances, clinical research, publications, and guideline development. (Bernard-Marty, 2004; Altundag, 2006; Genentech, 2015)

Treatment Advances In breast cancer, treatment innovation has plateaued in recent years. Some therapies developed 20 to more than 35 years ago, for example, remain part of the standard of care for some patient types. (ASCO BC, 2015; NCCN guidelines® for Breast Cancer V.3.2015, 2015; Klijn, 1985; Crighton, 1989; Sherman, 1979; Cole, 1971; Santa-Maria, 2015) Of the 8 therapies approved in the last decade, only 5 were targeted agents and 3 were chemotherapy agents. (NCI lapatinib, 2015; NCI pertuzumab, 2015; NCI ado-trastuzumab, 2015; NCI everolimus, 2015; NCI bevacizumab, 2015; NCI paclitaxel,

2015; NCI eribulin, 2015; FDA ixabepilone, 2015) One of the 5 targeted agents, bevacizumab, received FDA approval in 2008 in combination with chemotherapy for patients with mBC. (NCI bevacizumab, 2015) In 2011, however, the FDA revoked approval after subsequent studies failed to confirm benefit, whereas the European Medicines Agency retained the indication. (NCI bevacizumab, 2015; EMA bevacizumab, 2015) Moreover, development of therapies for mBC has not progressed at the same pace for all mBC tumor subtypes. In fact, over the last decade, the majority of new therapies have been for HER2+ cancers, which represent <15% of total mBC (Howlader, 2014), and there have been no therapy advances for TNBC (Figure 3.9). (NCI lapatinib, 2015; NCI pertuzumab, 2015; NCI ado-trastuzumab, 2015; NCI everolimus, 2015; NCI bevacizumab, 2015; NCI paclitaxel, 2015; FDA ixabepilone, 2015) Not including bevacizumab, as discussed above, only 3 targeted therapies were introduced from January 2010 through December 2014, of which 2 were for HER2+ mBC. (NCI bevacizumab, 2015; NCI pertuzumab, 2015; NCI ado-trastuzumab, 2015; NCI everolimus, 2015)



Figure 3.9

Approved Therapies for mBC Based on Phase III Registrational Trials*, January 2004–December 2014

Lapatinib, 2015; NCI lapatinib, 2015; NCI pertuzumab, 2015; NCI ado-trastuzumab, 2015; NCI everolimus, 2015; NCI eribulin, 2015; FDA ixabepilone, 2015; NCI paclitaxel, 2015

| Subtype | Therapy Regimen | MOA | First Approval, Year | mBC Patient Setting [†] |
|---------------|--|--------------|----------------------|--|
| HER2+ | lapatinib | Targeted | 2007 | Second-line therapy in combination with capecitabine following prior treatment |
| | pertuzumab | Targeted | 2012 | In combination with trastuzumab and docetaxel for patients who have not yet received anti-HER2 therapy or chemotherapy |
| | ado-trastuzumab emtansine | Targeted | 2013 | Single-agent for second-line therapy following prior treatment with trastuzumab and a taxane |
| HR+/HER2- | everolimus | Targeted | 2012 | In combination with exemestane in postmenopausal women after failure of treatment with letrozole or anastrozole |
| Not specified | eribulin mesylate | Chemotherapy | 2010 | Following prior treatment with at least 2 chemotherapeutic regimens for mBC; prior treatment should have included an anthracycline and a taxane in either the adjuvant or metastatic setting |
| | ixabepilone | Chemotherapy | 2007 | Alone or in combination with chemotherapy for treatment resistant mBC or locally advanced breast cancer |
| | paclitaxel- protein-bound, albumin-bound | Chemotherapy | 2005 | After failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy |

*Table includes new therapies based on the first mBC indication approved. Line extensions or expanded indications within mBC added after initial approval are not included. Bevacizumab was approved for mBC in 2008, but approval was revoked in 2011 in the US. (FDA 2006-2009, 2015; NCI bevacizumab, 2015) Outside the US, bevacizumab is used in combination with chemotherapy for the treatment of mBC. (EMA bevacizumab, 2015)

[†]Per US label.

Note: There have been FDA approvals for new treatments since December 2014 that are not captured in this table.



Research: Clinical Trials The relative pace of innovation in mBC seems to have slowed from 2007 to 2011 as evidenced by changes in the number and focus of clinical trials (Figure 3.10). From the limited data available on estimates of clinical trial activity in breast cancer from a review of trials started between January 2007 and December 2011, some trends were identified: (Crucefix, 2015; Parker, 2012; Dogan, Breast Cancer Res Treat 2013)

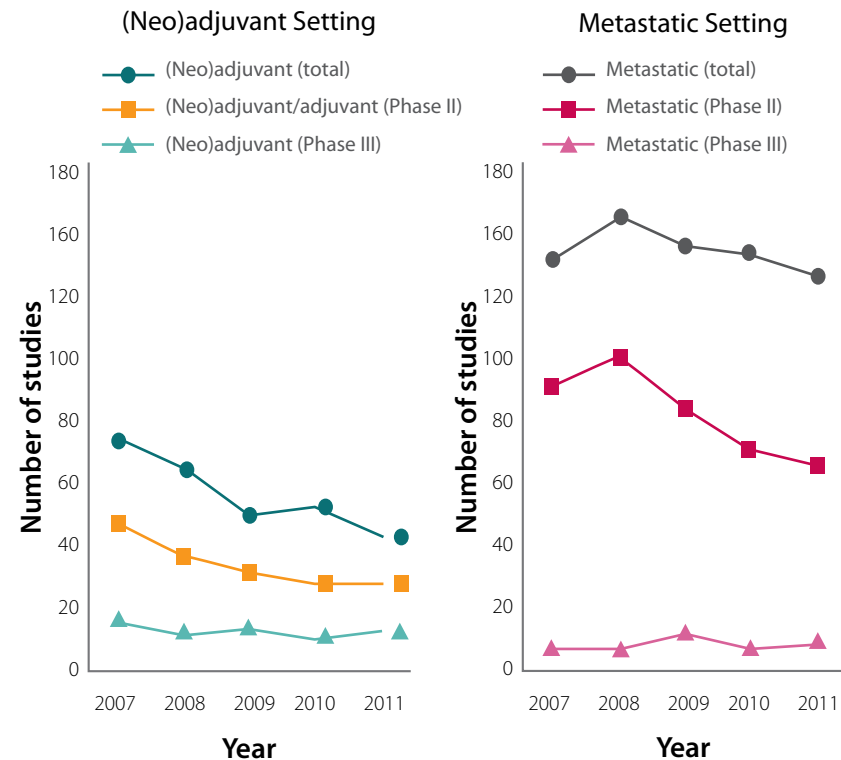
- Decreases in the number of patients enrolled (excluding outliers)
- Decreases in clinical trials focused on conventional and targeted therapies
- Decreases in small, Phase II trials in unselected populations
- Decreases in Phase II trials
- Increases in trials focused on symptom management

In mBC specifically, a general decline had also been observed, with a decrease in the number of Phase II trials from 2007–2011. (Dogan, Opin Oncol 2013) However, in recent years, the number of Phase III trials that have started enrolling patients has increased. Most of these trials are ongoing and will be discussed in the next chapter. (ClinicalTrials.gov, 2015)

Figure 3.10

Distribution Between Phase II and Phase III Trials in the (Neo)adjuvant and Metastatic Settings, 2007–2011

Dogan, Curr Opin Oncol, 2013



Note: Data are provided through 2011 and may not be generalizable to more recent years.

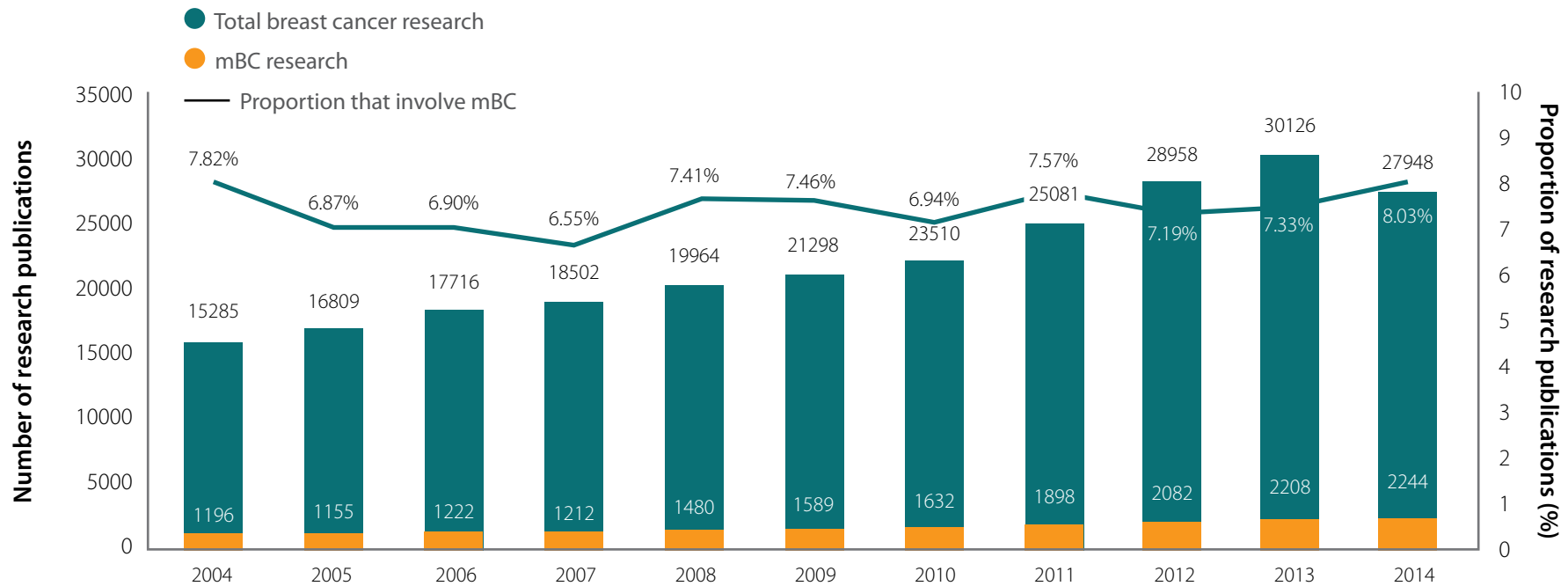


Publications and Congress Presentations A look at the publication landscape also provides some perspective on the challenges in advancement for mBC treatment in terms of the information available to clinicians. Over the last decade, publication focus for mBC has been

consistently low. And, there has been no change in this trend: only about 7% of all breast cancer publications per year are related specifically to mBC (Figure 3.11).

Figure 3.11

Number and Proportion of Research Publications Annually in mBC, 2004–2014



Database: SciFinder®. Key Words: "Advanced" OR "Stage IV" OR "Metastatic" + breast cancer. Year Range: 2004-2014.



Further analysis of conference presentations on mBC over the last 5 years (See Appendix 3.2 for search methodology) included interventional trials in the form of Phase II and III preapproval clinical trials. Frequency of searched terms among abstracts is shown in Figure 3.12 and the frequency of subtypes mentioned in abstracts is shown in Figure 3.13. Of the subtypes mentioned, HER2+ was the most frequently mentioned, which is consistent with where the most treatment advances have occurred in the last decade. Reduced mention of the other subtypes suggests that investment in research in those areas still lags behind.

Figure 3.12

Frequency of Key Terms in mBC Conference Abstracts

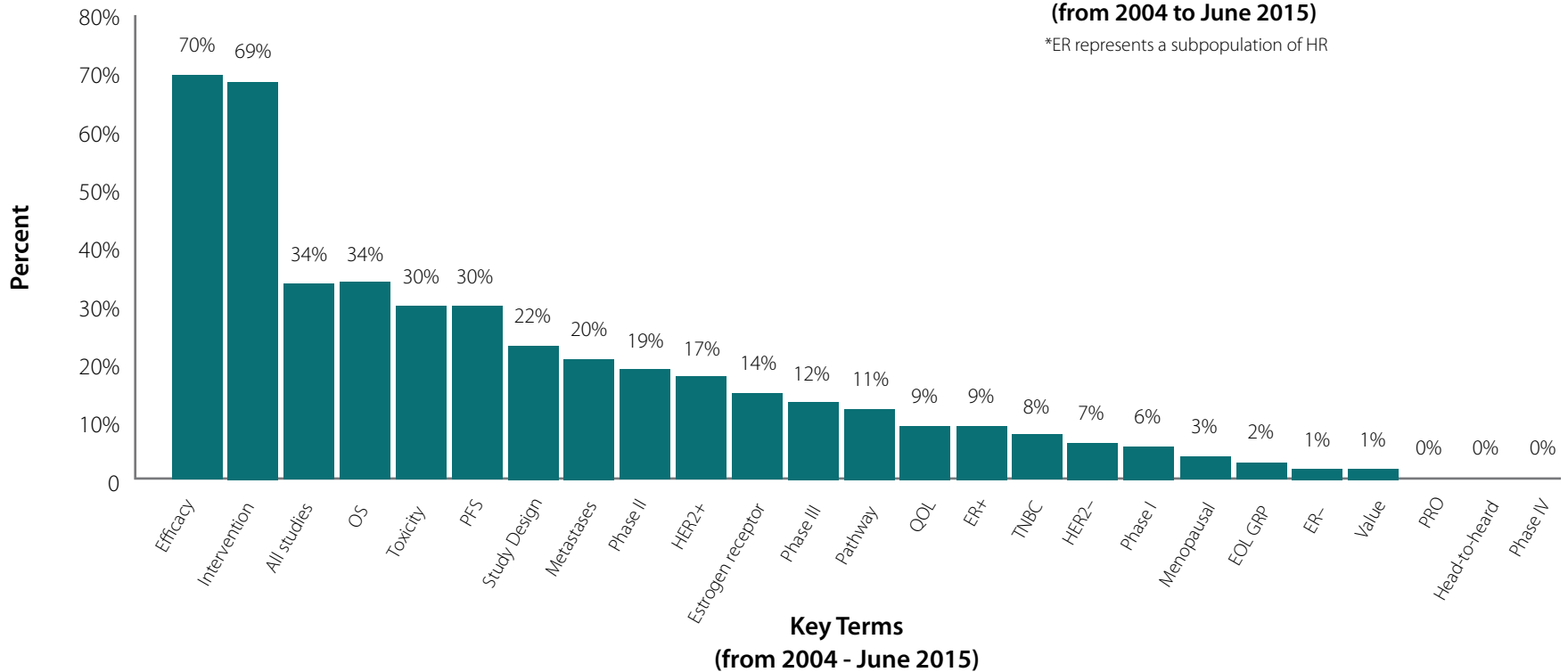
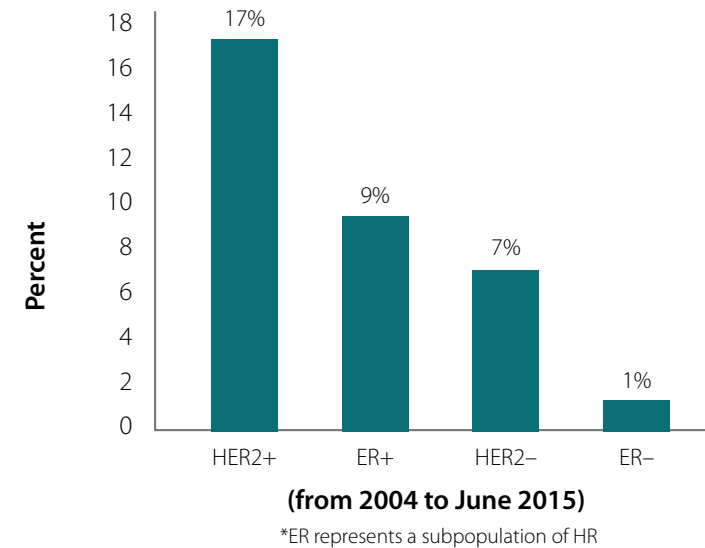


Figure 3.13

Frequency of Subtypes in mBC Conference Abstracts



// There is no proven value of routine ‘screening’ tests for metastatic disease in asymptomatic early breast cancer patients. However, the available data are from a time when neither biological therapy nor effective... and less invasive... loco-regional therapeutic techniques... were available. In addition, new detection techniques are now available... that may allow the detection of very early metastatic disease. Therefore, new studies are needed to evaluate the role of early diagnosis of metastatic disease in the current context. //

Fatima Cardoso, MD, et al. Annals of Oncology, 2012

Guidelines In addition, there is a need for more comprehensive and sophisticated guidelines—including level of detail, scope, and specificity of data for mBC—to help guide physician treatment decisions (Figure 3.14). (Coates, 2015; Cardoso, 2012) For example, although mBC was included in general breast cancer guidelines, including the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), international guidelines specifically concerning advanced (ie, metastatic) breast cancer did not exist until 2012. (NCCN guidelines® for Breast Cancer V.3.2015, 2015; Cardoso, 2012) There are opportunities for improvement in mBC guidelines, such as in the care of brain or bone metastases, and optimal sequencing of treatments. (Cardoso, 2014)

Figure 3.14

Topic Areas in Guidelines: eBC vs mBC

Coates, 2015; Cardoso, 2014

| eBC (2015 St. Gallen) | mBC (2014 ABC) |
|--|--|
| <ul style="list-style-type: none"> • Surgery • Radiation therapy • Pathology • Adjuvant therapy • Neoadjuvant therapy • Use of bisphosphonates • Elderly vs young patients • High risk mutations • Breast cancer diagnosed during pregnancy • Pregnancy after breast cancer • Male breast cancer • Lifestyle factors | <ul style="list-style-type: none"> • General recommendations • Assessment guidelines • General treatment guidelines • ER+/HER2- mBC • HER2+ mBC • Chemotherapy and biological therapy • Specific sites of metastases • Supportive and palliative care • Metastatic male breast cancer |

Note: Dates refer to the year the guidelines were published.

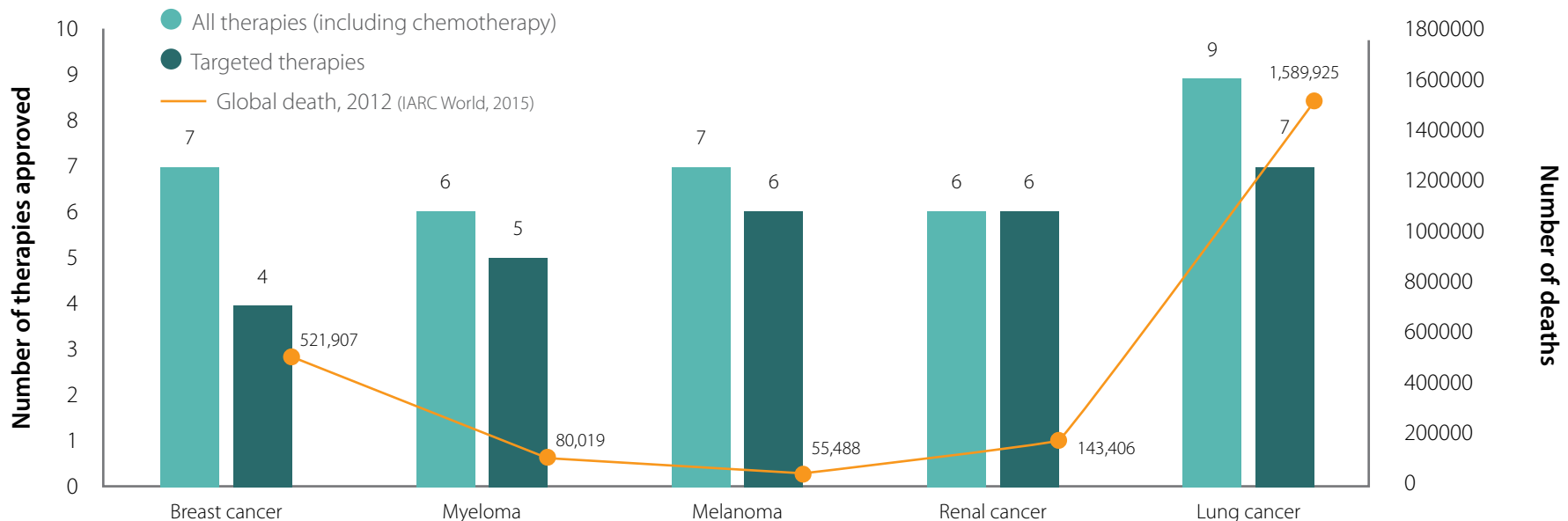


B The pace of innovation in mBC has lagged behind other tumor types over the last decade

Availability of New Therapies Taking into account the new therapies that have been developed in the past decade, innovation in mBC appears to be lagging behind that of several other tumor types. Figure 3.15 illustrates, from 2005 to 2014, that there were 6 new targeted therapies approved for melanoma and 7 new targeted therapies approved for lung cancer, while there were only 4 targeted therapies approved for mBC.

Figure 3.15

FDA Approvals of Therapies in Selected Metastatic Tumor Types, 2005–2014 and Global Deaths Due to Tumor Types (of Any Stage) in 2012



Note: Figure includes new therapies based on the first indication approved. Line extensions or expanded indications added after initial approval are not included. Agents counted in each bar graph are as follows: Breast cancer: ixabepilone, lapatinib, paclitaxel protein-bound particles for injectable suspension, eribulin, everolimus, pertuzumab, ado-trastuzumab emtansine. Bevacizumab was approved for mBC in 2008, but approval was revoked in 2011 in the US. Outside the US, bevacizumab is used in combination with chemotherapy for the treatment of mBC. As such, it is not counted in the breast cancer bar graph. In the EU, approved therapies for mBC in the last decade include bevacizumab, docetaxel, paclitaxel, lapatinib, everolimus, eribulin, pertuzumab, and trastuzumab emtansine. (EMA assessments, 2015). Myeloma: bortezomib, doxorubicin, lenalidomide, thalidomide, carfilzomib, pomalidomide; Melanoma: vemurafenib, peginterferon alfa2b, ipilimumab, nivolumab, pembrolizumab, trametinib, dabrafenib; Kidney cancer: pazopanib, bevacizumab, everolimus, temsirolimus, sunitinib, axitinib, sorafenib; Lung cancer: erlotinib, pemetrexed, bevacizumab, crizotinib, paclitaxel protein-bound particles for injectable suspension, ramucirumab, ceritinib, crizotinib, afatinib.



Since 2014, innovation in other tumor types has significantly increased. For example, noteworthy developments that occurred in 2015 included:

- Myeloma: Approval of a new class of drug, FDA submission for a novel monoclonal antibody, and positive results from Phase III studies that may result in further approvals (FDA 2015 news, 2015; Daratumumab, 2015; ASCO ELOQUENT, 2015)
- Melanoma: Significant progress in the introduction of immunotherapies, as well as targeted therapies for specific subtypes. (FDA 2015, 2015) Recent Phase III trial data demonstrate improvement in OS from novel combinations of targeted therapies (*ScienceDaily*, 2015)
- Advanced renal cell carcinoma: A new targeted therapy was granted fast track designation by the FDA and 2 new drugs recently had positive results in Phase III studies (PR Newswire, 2015; Eurekalert, 2015; Cabozantinib, 2015)
- Lung cancer: 2 additional targeted therapies have been approved, including an immunotherapeutic agent; 2 other agents undergoing FDA review, including immunotherapy (FDA 2015, 2015; Nivolumab, 2014; Necitumumab, 2015; Pembrolizumab, 2015)

It should also be acknowledged that since 2014, there have been advances in mBC, such as the increased understanding of the cyclin-dependent kinases 4 and 6 (CDK4/6) and phosphoinositide 3-kinase (PI3K) classes of drugs, which are of interest because of their novel mechanisms of action. (Yamamoto-Ibusuki, 2015)

Disease Understanding The lag in innovation in mBC in the last decade can also be characterized in other ways beyond the quantity of new treatments approved. The advances in disease understanding, the level of innovation and transformative potential of new treatment approaches (such as immunotherapy), and advances in precision medicine have accelerated in metastatic melanoma and metastatic lung cancer compared with mBC (Figure 3.16). (Masters, 2015)

Ultimately, other tumor types owe much to the groundbreaking advances made in mBC, where trastuzumab “made clear the promise of personalized medicine” and “marked the dawn of a new era of cancer treatment by bringing an emerging understanding of cancer genetics out of the laboratory and to the patient’s bedside.” (FDA development, 2015). Although the rate of innovation in other tumor types has outpaced the rate in mBC in recent years, there has been progress in applying genomic discoveries and gene expression profiles to further classify heterogeneous breast cancers into specific subgroups and to parse the prognosis, pathological features, and developmental behavior of these tumor subgroups—especially for TNBC. However, personalized medicine in mBC based on genomic technologies are only just beginning to have an impact on clinical practice. (Ellsworth, 2010) As noted by the 2015 ASCO recommendations, there has been no additional innovation in the use of biomarkers to guide mBC systemic therapy decisions beyond ER, PR, and HER2. (Von Ponzak, 2015)



Figure 3.16

Highlights of a Decade of Understanding of Disease in Select Tumor Types Through December 2014

ASCO BC, 2015; Bonotto, 2104; ESMO, 2015; Korpanty, 2014; FDA 2015, 2015; FDA 2012, 2015; FDA 2011, 2015; FDA 2010, 2015; FDA 2006-2009, 2015; Goodman, 2015; Masters, 2015; FCR, 2015

● Low or no innovation ● Medium innovation rate ● High innovation rate

| | mBC | Melanoma | Lung Cancer |
|---|---|------------------------------------|-------------------------------|
| Advances in clinically relevant subtype classifications | ● No major validated advances beyond the HR+ (luminal A or B), HER2+, TNBC for more than a decade | ● BRAF, RAS, NF1, triple wild-type | ● ALK, EGFR, MET, ROS-1, KRAS |
| Treatments for new pathways or targets* | ● | ● | ● |
| Companion diagnostics for precision medicine | ● | ● | ● |
| Immunotherapy | ● Being studied, mainly in TNBC | ● New treatments approved | ● New treatments approved |
| Number of breakthrough therapy designations† | 2 | 2 | 10 |

*Qualitative assessment.

†Breakthrough therapy designation by the FDA started in 2013. Breakthrough therapy designation is granted when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, addressing an unmet need for a serious or life-threatening condition. Breakthrough therapy designation count includes all agents through September 15, 2015. (FCR, 2015; FDA breakthrough, 2015)



Chapter 4: Focus for the Future

- Research efforts must be accelerated to transform outcomes in mBC
- Additional advances rely on realizing the promises of precision medicine and improved understanding of the genomic underpinnings of mBC
- Improving knowledge of mBC in specific populations, such as TNBC, progressive HR+ mBC, older women, men, and oligometastatic disease, is needed
- In recent times, there has been a substantial increase in the number of late-stage trials of investigational drugs in mBC
 - The largest number of phase III trials are in HR+/HER2- mBC
 - TNBC has the largest number of investigational drugs in development, reflecting the high unmet need
 - Apart from new drugs, new approaches to sequencing and combinations are also needed
- Other areas for future innovation include
 - New types of patient-relevant endpoints in clinical trials
 - Better registries and real-world data generation
 - Demonstration of the value of new treatments
- Research alliances and partnerships are critical to improve outcomes for patients with mBC

A Acceleration of research efforts is required to transform outcomes in patients with mBC

Overall, the current challenges in achieving progress in mBC can be thought of in terms of a failure to attain the aspiration of turning mBC into a chronic disease with the potential to achieve lasting remissions. Significant change can occur in breast cancer in the mBC space, and we need to intensify our efforts to accelerate innovation.

In a survey, 20 breast cancer expert oncologists at centers in Europe and the United States were asked to provide their perspectives on the difficulties they face in caring for patients with mBC and their hopes for the future. (TRM Oncology EPIC Report, 2015) Although they acknowledged

the major inroads that have been made in the treatment of mBC—including recognition of the overexpression of HER2 as an oncogenic driver, development of multiple lines of targeted therapy to maintain suppression of HER2+ mBC, the addition of targeted therapies to supplement endocrine therapy for HR+ mBC, and recent developments in the understanding of the heterogeneous cluster of subtypes of TNBC—they agreed that many challenges remain. (TRM Oncology EPIC Report, 2015) These challenges speak to the goals many clinicians who treat mBC aspire to overcome, as reported in the survey: (TRM Oncology EPIC Report, 2015)

- Despite advances, >500,000 women died from BC in 2012. (IARC World, 2015) In the absence of cure, experts hope to turn mBC into a disease that people die with, not from



“ We need to understand how cancer reacts to therapeutic influences in order to individualize—patient by patient—the combinations of drugs that might ultimately, in combination, lead to disease control, as has been accomplished in the treatment of HIV. ”

Dr. Matti Aapro, IMO Clinique De Genolier, Expert Perspectives on Current Challenges and Aspirations in mBC, TRM Oncology EPIC Report, July 2015

- Turning HER+ or HR+ mBC into a chronic disease brings challenges with tolerability and adherence to ongoing therapy, in addition to questions on costs of care
- Survival in TNBC is the lowest across all the subtypes and represents an area of urgent need
- Despite several treatment options in HER2+ or HR+ mBC, resistant disease emerges and the disease will progress
- There is now a large population of patients who have been treated with multiple lines of therapy for many years. Evidence-based medicine is challenging because clinical trial experience is mostly limited to earlier therapeutic lines

Efforts to address these challenges can be divided into a further understanding of the underlying mechanisms of the breast cancer disease process, including genomics, immune profiling, and further molecular subtyping; increased investigation into specific mBC patient populations, including those with limited metastases (ie, oligometastatic disease), older women and men, TNBC, and patients with relapsed HR+ BC; advances in treatment, including development of new targeted therapies and sequencing of therapies; and finally, innovations in the way that we conduct clinical trials, collaborate on research, and demonstrate the value of new treatments.

The recognition that much more needs to be done in mBC is gaining momentum, such that over one-quarter of the Breast Cancer Research Foundation’s annual grants are now focused on mBC. (BCRF research, 2015) Key focus areas include understanding the biology driving the why and how of metastasis, development of new treatments, clinical trials for new drugs or combinations, and correlative studies on biomarkers to predict which breast cancers are more likely to spread. (BCRF research, 2015) Susan G. Komen also extensively funds research focused on mBC, and in 2015 nearly half of their new research grants to young investigators were in this disease area. (Susan G. Komen)

Precision Medicine

Arnedos, 2015

Advances in genomics may provide valuable insight that could be applied to personalize therapy for patients with mBC through various applications, including:

- Identification of additional drivers of oncogenesis in mBC, such as ESR1, ERBB2, PIK3CA, AKT1, FGFR1, etc
- Characterization of the resistant clones (eg, ESR1 mutations)
- Characterization of DNA repair defects that accumulate from oncogenesis to residual disease to resistant lethal disease (eg, BRCA1, BRCA2, ATM, ATR, Proto-Oncogene, MDM), etc
- Characterization of the mechanisms of immune suppression



“ The technologies that have advanced the fields of genomics (the study of genes) and proteomics (the study of proteins) are the foundation of precision medicine and continue to evolve. Emerging technologies in tumor metabolomics (the study of how tumors utilize energy) and liquid biopsy methods (measuring tumor proteins or genetic material in blood or other bodily fluids) will further enhance our ability to individualize screening and diagnosis, treatment and tumor monitoring. ”

Breast cancer experts, AACR 2015: Progress, Promises and Future Challenges in Cancer Research, Breast Cancer Research Foundation, May 2015

B Advances in precision medicine and genomic understanding are required

Thanks to parallel sequencing of hundreds of breast cancer samples, combined with data from a large-scale investigation of the copy number alterations linked to gene expression abnormalities, we now have a more comprehensive catalog of the mutations underlying breast cancer. (Shah, 2012; Stephens, 2012; Banerji, 2012; Curtis, 2012) A highly complex picture of the genetic events driving pathogenesis has emerged, including the identification of significantly mutated genes (SMGs) for each of the major subtypes of breast cancer. (Ellis, 2013) This may help to improve patient management and treatment. (Ellis, 2013) However, much of the research to date has been limited to eBC, due to the difficulty in profiling mBC as a result of treatment-exacerbated molecular evolution and acquisition of new molecular aberrations, thereby limiting development of precision medicine in mBC. (Zardavas, 2014) However, recent efforts have been initiated to close this gap, with the goal of implementing precision medicine in mBC. (Zardavas, 2014) For example, AURORA (Aiming to Understand the Molecular Aberrations in Metastatic Breast Cancer) and the Metastatic Breast Cancer Project (MBC Project) are both mBC

molecular profiling program meant to uncover clinical gaps and gaps in knowledge. (Zardavas, 2014)

Many oncologists aspire to a future when modern sequencing technologies and a repertoire of targeted agents can be leveraged to personalize therapy to the exact genotype(s) of the tumor and metastases. (TRM Oncology EPIC Report, 2015) ASCO has recognized the importance of using biomarkers appropriately in guiding decisions for patients with mBC and has published guidelines on the available evidence. (van Poznak, 2015)

Metastatic Breast Cancer Project

MBC Project, 2016

Another collaborative effort is the Metastatic Breast Cancer Project being undertaken by the Broad Institute of MIT and Harvard, a nonprofit academic research institution. The project aims to create a national database of patients' blood and tumor samples, along with their medical records to be shared with the National Institutes of Health and the cancer research community for use in other genomic and molecular studies.



The AURORA Program

Zardavas, 2015; Zardavas, 2014; I-SPY 2 trial, 2015

The AURORA program is an academia-driven initiative that aims to boost genomic and clinical knowledge generated from mBC patients. This initiative in mBC may be considered comparable to studies in eBC, such as the I-SPY2 trial, where genomics are well characterized to individualize treatment approaches.

The AURORA program will focus on newly diagnosed or first-line patients with mBC. These patients will be divided into the following groups:

- Patients with mutations where action can be taken (downstream-targeted clinical trials with continuation until disease progression)
- Patients with mutations where no action can be taken (standard of care)

Data collection includes:

- Metastatic lesion biopsy at study entry for targeted gene sequencing and ribonucleic acid (RNA) sequencing
- Primary tumor from archival samples at study entry for targeted gene sequencing and RNA sequencing
- Blood samples at study entry for targeted gene sequencing and RNA sequencing
- Plasma/serum samples at study entry, then every 6 months, up to 10 years
- Clinical outcomes at study entry, then every 6 months, up to 10 years

This and other ongoing research initiatives into the genetic mutations; mechanisms of resistance; and classification using immunologic, genomic, or biomarkers are to be supported and encouraged in the hopes that they will open new avenues for optimizing treatment.

The pressing need for ongoing research has been recognized by the FDA, along with the American Association for Cancer Research (AACR), the American Society of Clinical Oncology (ASCO), and the Breast Cancer Research Foundation (BCRF). (FDA Workshop, 2015) Together, these organizations held a public workshop for international breast cancer experts, government officials, industry representatives, and patient advocates, to discuss the development of an international genomically driven trial to test multiple agents in patients with mBC. (FDA workshop, 2015) Some of the recommendations from the workshop include

leveraging knowledge and experience from trials in other cancer types to improve breast cancer clinical trials, including the use of genomics and liquid biopsies. Other opportunities are statistical considerations; exploring combination targeted therapy; methods of co-developing 2 or more new agents; identifying molecular pathways that would be worthwhile to target; optimizing data collection; and use of companion diagnostics. (Beaver, 2015; Solit, 2015; Velculescu, 2015; LaVange, 2015; Norton, 2015; Wagle, 2015; Amiri, 2015; Perou, 2015; Hudis, 2015; Mansfield, 2015)



C Better understanding of mBC in specific populations is essential to inform clinical advances

Triple-negative mBC The recent identification and classification of at least 6 separate molecular TNBC subtypes, each with distinctive biologies, has been 1 area of advancement. (Lehmann, 2015) Moreover, some TNBC molecular subtypes have been shown to be more sensitive to specific treatments than others. (Lehmann, 2015) For example, emerging data for poly (ADP-ribose) polymerase (PARP) inhibitors suggests benefit in women with BRCA mutant TNBC (approximately 10%-20% of all TNBC patients). (Lehmann, 2015) Basal-like breast carcinomas, which characterize 2 of the TNBC molecular subtypes, (Mancini, 2014) frequently harbor defects in DNA double strand break repair due to dysfunction in genes, such as

Potential TNBC Subsets

Mancini, 2014; Le Du, 2015

One novel approach is to target the programmed-cell-death-1 (PD-1) receptor and programmed-cell-death-ligand 1 (PD-L1) pathway, a potent mechanism by which immunogenic tumors evade host immune response. PD-L1 is overexpressed in 20% of TNBC and appears to be a biomarker predicting response rate.

Additionally, it is yet to be determined if the new genomic classifications of TNBC will translate into positive effects on treatment decisions and outcomes. A case where this might be important is with BRCA1/2-mutated TNBC, which defines a subset that derives better benefit from platinum therapies and might be a target population for PARP inhibitors in the future. Ultimately, therapeutic development needs to be optimized based on path identification, modulation, and validation.

“ Breast cancer is increasingly fragmented into smaller molecular subpopulations and a successful coupling of patients with the corresponding targeted treatment based on the genotype of their disease will be essential. ”

*Dimitrios Zardavas, MD, et al. British Journal of Cancer, 2014
Reprinted by permission from Macmillan Publishers Ltd
on behalf of Cancer Research UK: British Journal of Cancer
(Zardavas D, et al. Br J Cancer. 2014;111:1881-1887.)*

BRCA1. (Lehmann, 2015) If present, this DNA repair defect makes tumors sensitive to PARP inhibition, which results in cell death and apoptosis. (Lehmann, 2015; Wahba, 2015)

Progression in HR+ mBC Experts recognize that progression is a common challenge in mBC across tumor types, but particularly for HR+ cancer. (TRM Oncology EPIC Report, 2015)

There is a need to identify and target additional escape pathways and to accumulate evidence to support new therapeutic approaches for addressing resistance to an endocrine therapy regimen which is the current standard in HR+ mBC. (TRM Oncology EPIC report, 2015, Yamamoto-Ibusuki, 2015) These approaches may have the potential to increase the duration of time that HR+ mBC can be controlled. Additionally, the occurrence of resistant mutations, such as ESR1 mutations after endocrine therapy, presents an area of further research. (Iwase, 2015; Baselga, 2012; Roy, 2009; Abemaciclib, 2015; Santa-Maria, 2015; Arnedos, 2015)



Women older than 65 years of age and men Certain populations are underrepresented in mBC, such as women 65 years of age and above and men. (de Glas, 2015; Kaufman, 2012; Yu, 2013) There remains a need for additional research to identify which patients should receive which treatments and to measure specific outcomes that are of special interest to these individuals (Figure 3.17).

Figure 3.17

Considerations in Other mBC Patient Populations

Johnson, 2013; de Glas, 2015; Zulman, 2011; Kaufman, 2012; Wildiers, 2007; Biganzoli, 2012; Guralnik, 1996; Kiderlen, 2014; Giordano, 2004; Nahleh, 2007; Masci, 2015; Yu, 2013

| mBC in Older Women | mBC in Men |
|--|---|
| Clinical trial exclusion criteria bias towards younger individuals | <1% of mBC cases |
| Physician bias | More likely to be HR+, less likely to be HER2+ |
| Lack of guidelines | Differences in OS in men vs women |
| Extrapolation of recommendations | Extrapolation of treatment recommendations from evidence in women |
| Variation within the older patient population | |
| Overall and relative survival have not improved compared with younger patients | |

Oligometastatic disease and surgery There is a distinctive subset of mBC patients who have “oligometastatic” disease, characterized by solitary or few detectable metastatic lesions that are usually limited to a single organ. (Pagani, 2010) These patients can achieve a complete response to endocrine, cytotoxic, targeted, or combination therapy and remain disease-free for a prolonged period. These patients may benefit from an intensified multidisciplinary team approach involving localized surgery, radiation, radiofrequency ablation, chemoembolization, and chemotherapy. (O’Shaughnessy, 2005; Tomiak, 1996; Pagani, 2010; Di Lascio, 2014)

Research is also ongoing to establish whether good survival outcomes can be achieved after resection of limited mBC sites, followed by aggressive systemic therapy. (Begg, 2015; Helwick, 2012) If positive, the results would have significant implications, but only for the management of a small group of patients, such as those presenting with stage IV breast cancer de novo with an intact primary tumor, or those who develop metastases in isolated, surgically resectable sites only. (Begg, 2015; Helwick, 2012)



// Control of metastatic cancer in particular is very difficult. Tumor cells no longer follow the rules that govern the function of normal cells which allow them to upregulate alternate pathways and develop resistance to inhibitory therapy. Through these mechanisms, a tumor metastasis can have a totally different molecular profile from the primary tumor and require a completely different treatment approach. //

Cynthia Huang, MD, Senior Director of Global Medical Affairs, Pfizer, October 2015

D A robust pipeline of multiple new drugs may bring options for mBC patients in the future

Note: Drugs discussed in this section are investigational. Efficacy and safety cannot be established until regulatory approval is received.

Recent years have seen a substantial increase in research and development of new therapeutic approaches for mBC subtypes.

For the HR+ subtype, a primary goal has been to optimize the initial therapy for metastatic disease and prevent endocrine resistance by targeting cross-talk mechanisms between ER signaling and growth factor signaling. (Yamamoto-Ibusuki, 2015) Other targets being evaluated in all subtypes include those that may be more specific to an individual's disease (eg, src kinases), androgen receptors or inhibitors of cellular machinery (eg, histone deacetylases [HDAC] and PARP inhibitors). (Hosford, 2014; Santa-Maria, 2015) Finally, another therapeutic approach currently under investigation, particularly for TNBC, is immunotherapy, which has revolutionized treatment for some other cancers (eg, melanoma).

(Masters, 2015)

While many of these drugs are still in the early stages of development, more than 20 open Phase III studies with 15 investigational drugs for mBC were identified on clinicaltrials.gov, accessed on September 30, 2015—excluding Phase III studies of drugs already approved for use in breast cancer (Figure 3.18).

Phase III activity is greatest for HR+/HER2- mBC, with the largest number of ongoing Phase III studies (a total of 13) encompassing 7 new drugs across 3 classes. Of the 3 classes represented, the cyclin-dependent kinase (CDK) inhibitor class is the most advanced, with 1 drug approved in 2015, followed by the PI3K and HDAC inhibitors. All Phase III trials in HR+/HER2- mBC continue to use endocrine therapy in combination with the new drugs.

The high unmet need in TNBC is apparent, given the number of investigational drugs in Phase III studies, as well as large, randomized, Phase II studies of over 100 patients. The investigational drugs for TNBC include PARP inhibitors, antibody drug conjugates, and PD/PD-L1 immunotherapies. Many of the drugs in development for TNBC target specific mutations or populations, such as BRCA mutation or androgen receptor-positive; some have taken a precision medicine approach by incorporating companion diagnostics.

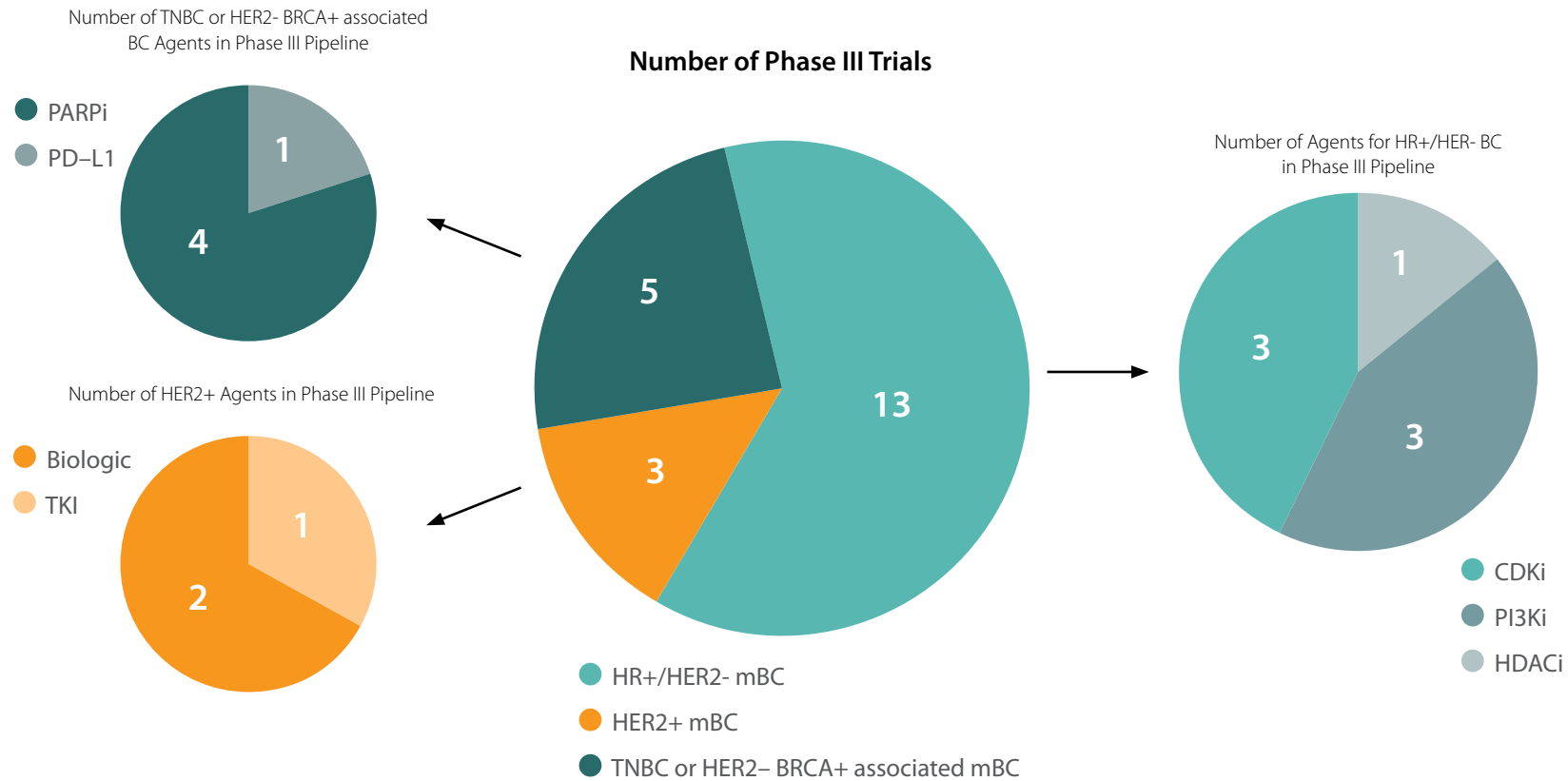
HER2+ mBC has the fewest ongoing Phase III clinical studies—a total of 3 studies including 3 drugs in 2 classes—following the initial spate of major therapeutic advances through the past decade. There are also new approaches being investigated in HER2+, such as vaccines and antibody-drug conjugates, but these are at an earlier stage in development.



Figure 3.18

Open, Interventional, Phase III Trials of Investigational Drugs in mBC by Subtype, ClinicalTrials.gov, September 15, 2015

See Appendix 3.3 for search methodology



Note: Investigational drugs are those that have not been approved for breast cancer as of the cut-off date of December 2014. This figure only includes open Phase III studies from which data are pending or positive. CDKi=cyclin-dependent kinase inhibitor; HDACi=histone deacetylase inhibitor; PARPi=poly(ADP-ribose) polymerase inhibitor; PD-L1=programmed-cell-death-ligand 1; PI3Ki=phosphoinositide-3 kinase inhibitor; TKI=tyrosine kinase inhibitor.



“ In 10 years, I hope to see more personalized therapy with predictive markers for targeted therapies or agents that will work extremely well in all patients. ”

Dr. Nadia Harbeck, Professor of Gynecology, Head of Breast Cancer, University of Munich

E New combinations and sequencing of treatments are needed to improve outcomes

There is a real need for understanding the optimal sequencing of treatment, since there are multiple ongoing trials and multiple new drugs being studied in Phase III that could be approved in the future. (Zelnak, 2015; Clinicaltrials.gov) For optimal sequencing, there needs to be better understanding of patient selection and biomarkers, new types of trials, and registries to track real-world patient experience longitudinally across multiple lines of therapy. (Zelnak, 2015; CMTF, 2015; Barrios, 2012) In addition, novel combinations with new drugs, such as double and triple combinations, are an emerging area of research and development that could improve outcomes further. (Santa-Maria, 2015; NCI two drugs, 2015)

F New types of patient-relevant trial endpoints are required for mBC

To date, there is a paucity of post-progression treatment information in Phase III trials, and we know that OS may be affected partially, or directly, by the treatments that follow progression. (Raphael, 2015; Verma, 2011) Also, many interventional trials in mBC patients are simply not designed with the capacity to detect OS as a primary outcome and, therefore, PFS has been used as a primary endpoint in some clinical trials. (Verma, 2011)

This focus on OS or PFS also excludes other endpoints that may be of interest, such as tumor outgrowth. (Verma, 2011) Incorporating patient-relevant endpoints that take into account extended time of disease control without loss of quality of life and help clinicians, payers, and patients assess the clinical meaningfulness of therapy based on effectiveness, patient reported outcomes (PROs), and end-of-life parameters, is essential. However, routine incorporation of PROs, for example, into Phase III clinical trials has not yet become widespread practice. (Beauchemin, 2014; Blinders, 2014)

“ The ABC Conference has been the greatest advance in that it creates a strong association of professionals and patients to participate in the difficult decision-making process for the best care of patients with mBC. ”

Dr. Matti Aapro, IMO Clinique De Genolier, Expert Perspectives on Current Challenges and Aspirations in mBC, TRM Oncology EPIC Report, July 2015



G Registries and real-world data are essential to improve understanding of mBC

In addition to further delineating subtypes and refining therapeutic targets, it is also essential that we gain greater understanding of the patient population with mBC to provide insight into a variety of aspects of care (Figure 3.19). In the United Kingdom, for example, a registry project

with the aim of accurately assessing what future cancer care would be required resulted in recommendations to all breast treatment units on data to be collected moving forward. (NCIN, 2015) We need to understand the true prevalence of mBC and the true recurrence from early to late disease, since most databases (eg, SEER in US) only capture data on patients with metastatic disease at initial diagnosis. (MBCN, 2015)

Figure 3.19

Sample of Registries in mBC

| RegistHER Tripathy, 2014 | NCT02315365 Clinicaltrials NCT02315365, 2015 | ESTHER Registry Study Clinicaltrials NCT02393924, 2015 | SystHERs Registry Tripathy, 2014 |
|---|---|--|--|
| Large, multicenter, prospective, observational study including >1000 patients with newly-diagnosed HER2+ mBC. Describes the natural history of disease and treatment patterns; explores associations between demographics and clinical factors, therapies, cardiac toxicities, and patient outcomes | Study on quality of life, work productivity, and healthcare resource utilization in mBC | Observes the different anti-cancer treatment regimens and their sequencing throughout the course of disease in patients with unresectable locally advanced or mBC and describes the clinical outcome for each treatment regimen, measured as PFS | Gains in-depth data on demographic, clinicopathological, and treatment patterns and their associations with clinical outcomes, PROs, and healthcare resource utilization. In addition, this registry will establish tumor tissue and DNA repositories for use in future translational research |



H It is important to demonstrate the clinical value of mBC therapies

With the potential of new therapeutic approaches being available to mBC patients in the future, it is important that these new treatments demonstrate clinical value.

The changing healthcare landscape has been accompanied by an increasing recognition of the need for a dialogue among all stakeholders—patients, manufacturers, providers, and payers—about the value of therapies, particularly in oncology. (Schnipper, 2015) This is reflected in recent physician-driven efforts by organizations, such as ASCO and the European Society for Medical Oncology (ESMO), to develop a specific framework to assess the value of cancer treatment options in a way that informs clinical care. (Schnipper, 2015; Cherny, 2015) Although still in the early stages, the dialogue around clinical value acknowledges the need to more systematically incorporate numerous elements that define clinical value, including unwanted variation in quality and outcome, harm to patients, waste and failure to maximize value, health inequalities and inequities, and failure to prevent disease. (Schnipper, 2015; Cherny, 2015) Additionally, any tools developed to help demonstrate the value of therapies would need to take into account different clinical scenarios, treatments, benefits, toxicities, and costs. (Helwick, 2015)

“ While the world expects therapeutic breakthroughs, the fact that significant amounts of money are spent for small gains is becoming universally unacceptable. ”

Helwick C. ASCO Post 2012;5(12):1-2. Reprinted with permission. © 2015 American Society of Clinical Oncology. All rights reserved.

I Research alliances and partnerships are critical to improve outcomes for patients with mBC

Academic, professional, and patient alliances are also recognized as crucial for optimal clinical development and patient management/education success. A need for better interactions between industry, oncologists, and specialists, and regulatory authorities is also recognized. The I-SPY 2 trial, for example, leverages an innovative public-private partnership to help screen promising new drugs for women with eBC. (About I-SPY 2) Such efforts are needed in mBC as well.

“ Collaboration between industry and the breast cancer community is essential to driving the understanding of breast cancer. It will help patients to get breakthrough medicines faster and make them more accessible. The collaborations allow us to learn from investigators and from patients. Several clinical trials to understand genomics and immune profile of tumors are ongoing and are a good example of such partnerships. ”

Maria Koehler, MD, VP, Oncology Strategy, Innovation and Collaboration, Pfizer, Board certified hematologist oncologist



Emerging Recommendations

Despite the challenges that have been encountered in the treatment of mBC, numerous opportunities exist to improve the treatment of these patients. Efforts during the last decade have created a significant body of knowledge that has elucidated pathways that drive breast cancer and potential targets for treatment. These efforts have also emphasized the fact that breast cancer is a heterogeneous disease that affects all populations in different, and sometimes disproportionate, ways. As such, the treatment paradigm must focus on a personalized approach for each patient, with aspirations to change mBC into a chronic disease with long-term remissions. Realistically, much more needs to be done to accomplish this, including:

- More targeted investment in mBC research to understand the biology and genomics of why and how cancer cells spread, and why and how some tumors become resistant to therapy
- More targeted investment in mBC research to identify better predictive biomarkers
- Translating findings regarding the biology, genomics, and biomarkers of mBC into individualized/personalized therapy
- Better clinical trial design to manage the complexity and heterogeneity of the tumor types and patient populations
- Collaborating to conduct clinical trials to identify and define combination treatments and or sequence of treatments
- Leveraging the use of technology to build population-based databases with real-time data to better estimate disease burden and unmet need to deliver personalized care
- Commitment to address global disparities observed in mBC as a result of geography, ethnicity, and other factors
- Engagement, empowerment, integration, and commitment from all stakeholders—research alliances, industry, government, academia, patients, and patient advocacy groups—to collaborate and focus efforts to reduce the burden of mBC



Glossary

5-year survival rate - The percentage of people in a study or treatment group who are alive 5 years after they were diagnosed with or started treatment for a disease

Adherence - The extent to which a patient continues on an agreed mode of treatment without close supervision

Adjuvant therapy - Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back

Advanced breast cancer - Breast cancer that has spread to other areas of the body and cannot be cured with treatment. In this report, “advanced breast cancer” and “metastatic breast cancer” are used interchangeably

ALK - A protein called anaplastic lymphoma kinase (ALK), which may be involved in cell growth. Mutated (changed) forms of the ALK gene and protein have been found in some types of cancer

Axillary lymph nodes - also known as armpit lymph nodes, work as filters for the lymphatic system

Biomarker - A biological molecule that is a sign of a normal or abnormal process, or of a condition or disease

BRCA - A gene that normally helps to suppress cell growth. A person who inherits certain mutations (changes) in a BRCA1/2 gene has a higher risk of getting breast, ovarian, prostate, and other types of cancer

Breakthrough Therapy designation - A process designed by the US Food and Drug Administration to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)

Breast cancer - Cancer that forms in the tissues of the breast; it occurs in both men and women, although male breast cancer is rare. Invasive breast cancer is a cancer that has spread from its point of origin in the breast duct or lobules to the surrounding normal tissue

Clinical trial (interventional) - Clinical trials are studies that test potential treatments in human volunteers or patients to see if they should be tested further or approved for use in the general population. However, they must first be studied in models or animals to determine the safety in testing in people – only then are treatments moved into trials. Clinical trials are an integral part of a product’s discovery and development and the data from these are required by regulatory agency, such as FDA before a new medicine could be commercially available

Alternatively, non-interventional clinical trial designs include studies measuring QoL, risk assessment, screening, and prevention

Companion diagnostic - A medical device which provides information that is essential for the safe and effective use of a corresponding drug or biological product

Compliance - The consistency and accuracy with which a patient follows a prescribed treatment regimen

Cyclin dependent kinase - Protein that controls cell cycle progression in all cells

de novo - In cancer, the first occurrence of cancer in the body

Early breast cancer (eBC) - Breast cancer that has not yet spread beyond the breast or axillary lymph nodes

Early-stage disease - Cancer that is early in its growth and has not yet spread to other parts of the body. Early stages may differ between cancer types



Economic burden - The impact of ill health on human welfare ie, the economic consequences of poor health

EGFR - A cell surface protein which epidermal growth factor binds, causing the cells to divide. Many cancer cells have abnormally high levels on their surfaces causing them to divide excessively in the presence of epidermal growth factor

End-of-life care - This is the care given to patients who are near the end of life and have stopped treatment. Care includes physical, emotional, social and spiritual support for both the patient and their family. The goal is to ensure that the patient is as comfortable as possible and may include palliative care

Estrogen receptor-positive (ER+) - Describes cells that have a receptor protein that binds the hormone estrogen

Evidence-based medicine - Evidence-based medicine uses the findings and results from research to inform decisions in a real-world clinical practice setting. The 4 steps to this are: formulate a clear clinical question from a patient case study, search the literature for relevant research articles, evaluate the evidence, and then implement the findings in clinical practice

Functional wellbeing - The ability of a person to perform usual daily living tasks and to carry out social roles

Genomics - The study of the complete genetic material, including genes and their functions, of an organism

GLOBOCAN - The Global Burden of Cancer Study conducted by the International Agency for Research on Cancer (IARC) and aims to provide contemporary estimates of incidence, mortality, and prevalence of major cancers for 184 countries

HDAC - Also called histone deacetylase, is an enzyme that removes a small molecule called an acetyl group from histones (proteins found in chromosomes). This changes the way the histones bind to DNA and may affect its activity

Healthcare professional - An individual who provides health services to healthcare consumers

Health-related quality-of-life (HR QoL) - The subjective perceptions of the positive and negative aspects of cancer patients' symptoms including physical, emotional, social, and cognitive functions, disease symptoms and side effects

Heterogeneous - Made up of elements or ingredients that are not alike

Hormone receptor-positive (HR+) - Describes cancer cells that contain either estrogen or progesterone receptors

Human epidermal growth factor receptor 2-positive (HER2+) - Describes cancer cells that have too much of a protein called HER2 on their surface

Incidence - The number of new cases during a designated period of time

Intolerance - Lack of ability to endure a stimulus over a period of continued exposure

Invasive breast cancer - Cancer that spreads from the breast to surrounding normal tissue

Joint decision making - Patients can actively participate with their clinicians in making choices about their care and treatment

Ki-67 Index - Measures how rapidly tumor cells are dividing. Results <10% indicate a low division rate, 10-20% are borderline, and >20% is considered a high division rate

KRAS - A KRAS protein involved in cell signaling pathways, cell growth, and apoptosis (cell death)

Loss of Exclusivity - LOE. Time when a drug or product has gone off-patent

Mammography - The use of film or a computer to generate a picture of the breast, used to diagnose and locate breast tumors



Median survival - The length of time from diagnosis until half of the patients are still alive. In a clinical trial, measuring the median survival is 1 way to see how effective a treatment is

Medical oncologist - A doctor who specializes in diagnosing and treating cancer. They are often the main healthcare professional in the case of a patient with cancer and may coordinate the treatment given by other specialists

Met - Cell surface receptors for hepatocyte growth factor

Meta-analysis - A process that analyzes data from different studies done about the same subject

Metastasis - The spread of a cancer from 1 part of the body to another

Metastatic breast cancer - Breast cancer that has spread to other areas of the body and cannot be cured with treatment

Mortality - Refers to the state of being mortal. Also used in medicine for death rate, or number of deaths in a certain group of people in a certain amount of time

Neoadjuvant therapy - Treatment given as a first step to shrink a tumor before the main treatment is given (usually surgery)

Nonadherence - The extent to which a patient doesn't continue on an agreed mode of treatment without close supervision

Oligometastatic disease - Characterized by solitary or few detectable metastatic lesions that are usually limited to a single organ

Oncology nurse - A nurse in the field of oncology who provides care for patients with cancer. Nurses monitor patients' physical conditions, may prescribe medication and administer chemotherapy

Overall survival (OS) - The length of time from either the date of diagnosis or start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive

Patient support group - A group of people all with similar disease who help and support each other by sharing experiences and information

Palliative care - The care given to improve a patient's quality of life. The goal is to treat the symptoms of a disease, side effects of treatment and any psychosocial issues related to the disease or treatment

PARP - An enzyme involved in many functions of the cell, including the repair of DNA damage

PD1/PD-L1 - Also called programmed death-1 pathway/programmed death ligand 1. Expressed by many cancer cells

PI3K - Also called phosphatidylinositol-3 kinase and PI3 kinase. An enzyme that transmits signals in cells and that helps control cell growth

Precision medicine - Uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease

Personalized medicine - A form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease

Phase II trial - A study that tests whether a new treatment works for a certain type of cancer or other disease

Phase III trial - A study that tests the safety and efficacy and how well a new treatment works compared with a standard treatment

Phenotype - The observable characteristics, at the physical or biochemical level, of an individual, as determined by the genes and environment

Pivotal trial - A study which presents the data used by regulatory agencies to decide whether to approve a drug



Placebo arm - Placebo is an inactive form of the treatment drug being investigated – the placebo arm of a clinical trial is used as a control to assess how effective or safe the treatment drug is

Progesterone receptor-positive (PR+) - Describes cells that have a protein to which the hormone progesterone will bind

Predictive - Anticipates whether a person's cancer will respond to a specific treatment

Prognosis - Likely course of disease

Progression - The course of disease as it becomes worse or spreads in the body

Progression-free survival (PFS) - The length of time during and after treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse

Psychosocial well being - The psychological and social components of a disease and its treatment. This includes mood, belief, coping mechanisms, and relationships with family and friends

Quality of life (QoL) - The measurement of a patient's sense of well-being and ability to carry out day-to-day activities

Radiation oncologist - A doctor who specializes in using radiation to treat cancer

Real-world data - Data used for clinical, coverage, and payment decision-making that are not collected in conventional randomized, controlled trials

Recurrence - Cancer that has recurred (come back), usually after a period of time during which the cancer could not be detected

Registrational study - Primary safety and efficacy studies that the relevant government health agency uses to decide whether or not to approve the investigational drug or new use of a marketed drug (see Pivotal trial)

Registry - Collects detailed information about patients and the treatments they receive, and stores it in a searchable computer database

Relapse - The return of a disease or the signs and symptoms of a disease after a period of improvement

Resistance to treatment - Does not respond to treatment

ROS-1 - Growth or differentiation factor receptor expressed by many solid tumors

Screening - Checking for disease when there are no symptoms

Side effect profile - All of the potential side effects that may be caused by the drug. A side effect is any undesirable effects from drug treatment that are not intended as part of the therapeutic effect

Stage III disease - Further subdivided into IIIA, B and C.

IIIA:

- 1) No tumor is found in the breast/tumour may be of any size and cancer is found in 4 × 9 axillary lymph nodes
- 2) The tumor is > 5 cm and small clusters of breast cancer cells are found in the lymph nodes
- 3) Tumor is > 5 cm and the cancer has spread to 1–3 axillary lymph nodes

IIIB the tumour may be any size and cancer has spread to the chest wall and/or to the skin of the breast and caused swelling/an ulcer. Also cancer may have spread to:

- 1) Up to 9 lymph nodes
- 2) The lymph nodes near the breast bone



IIIC: no tumor is found in the breast or the cancer be of any size. Cancer may have spread to the skin and caused swelling/ an ulcer/spread to the chest wall. Also cancer has spread to:

- 1) 10 or more lymph nodes
 - 2) Lymph nodes above or below the collarbone
 - 3) Axillary lymph nodes and lymph nodes near the breastbone.
- Cancer that has spread to the skin of the breast may also be inflammatory breast cancer. Stage IIIC is either operable or inoperable

Statistical significance - A mathematical measure of difference between 2 groups that is greater than what might be expected to happen by chance alone

Subtype - Describes the smaller groups that a type of cancer can be divided into, based on certain characteristics of the cancer cells

Supportive care - The care given to improve a patient's quality of life. The goal is to treat the symptoms of a disease, side effects of treatment and any psychosocial issues related to the disease or treatment

Surgeon - A doctor who operates on a patient by removing or repairing parts of the body

Systematic literature review - Rigorous and standardized methods are used to select and assess articles, which are usually peer-reviewed publications – all focused on a specific topic that try to answer a specific research question. A meta-analysis may be performed as part of the review, which is a quantitative summary of the results

Systemic therapy - Treatment using substances that travel through the bloodstream, reaching and affecting cells all over the body

Targeted therapy - A type of treatment that uses drugs or other substances to identify and attack specific types of cancer cells with less harm to normal cells

Therapeutic goal - The outcomes expected relating to the treatment of disease

Drug toxicity - The extent to which a drug is harmful or poisonous

Triple-negative breast cancer (TNBC) - Breast cancer cells that do not have estrogen receptors, progesterone receptors, or large amounts of HER2/neu protein

US Centers for Disease Control (CDC) - CDC works to protect America from health, safety and security threats, both foreign and within the US. CDC is the nation's health protection agency and fights to save lives and protect people from health threats



Steering Committee Members

Fatima Cardoso, MD

Chairperson

European School of Oncology and Breast Unit,
Champalimaud Clinical Center
Lisbon, Portugal



Dr. Cardoso is the Director of the Breast Unit at Champalimaud Clinical Center, Lisbon, Portugal. Her medical degree is from University of Porto, Portugal, with fellowships at Jules Bordet Institute (IJB), Brussels and MD Anderson Cancer Center, Houston. She completed 10 years as Assistant Professor at IJB and was a scientific director of TRANSBIG (EU Framework VI). Currently, she is a member of the ESMO Board of Directors & Chair of National Representatives Committee, part of the EORTC Board of Directors & Chair of EORTC-Breast Group, ESO Breast Cancer Program Coordinator and Chair of the Advanced Breast Cancer International Consensus Guidelines, ASCO International Affairs and Breast Cancer Guideline Committees. Her research interests include biology of breast cancer, prognostic and predictive markers, and new anticancer agents.

Marc Beishon

Cancer World, European School of Oncology
London, United Kingdom



Marc Beishon is a freelance health, science and technology writer. He has worked for the European School of Oncology's Cancer World magazine since 2004 and is a member of the advocacy committee at the 2015 Advanced Breast Cancer conference in Lisbon.

Maria João Cardoso, MD, PhD

Champalimaud Clinical Center, Breast Unit
Lisbon, Portugal
Mama Help
Porto, Portugal



Maria João Cardoso was appointed as Head Breast Surgeon at the Champalimaud Breast Unit in 2011. Her undergraduate and postgraduate studies were undertaken at the Porto Faculty of Medicine. She has dedicated her career to breast surgery and started her training in oncoplastic surgery at the Institut Gustave Roussy in France. From 2007 to 2010 she was Clinical Director of the S. João Hospital Breast Unit in Porto and from 2004-2010 she was a member of the Ethics Committee at the same hospital. She holds a PhD in Medicine from University of Porto with the topic of objective evaluation of aesthetic results in breast cancer conservative treatment. From 2006 to 2011 she was Assistant Professor of the Department of Surgery of the Porto Faculty of Medicine. Dr MJ Cardoso is co-coordinator of the Breast Research group at INESC Porto with Professor Jaime Cardoso. As of 2012, she has published more than 30 papers in international journals as first author and has also co-authored more than 80 full communications in major international conferences. She is a member of the editorial board of The Breast journal and a reviewer of several international journals. One of her main interests is quality of life of breast cancer patients and she is the president of Mama Help a Support Centre for Breast Cancer Patients. She is a member of the board of the Portuguese Society of Senology.



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“CJ” (Dian) Corneliusen-James

METAvisor
Annapolis, USA



METAVIVOR



Following graduate school, “CJ” (Dian) Corneliusen-James joined the United States Air Force and over the next 24 years served in a host of military intelligence positions around the world. Retiring as a Lieutenant Colonel, CJ began a second career at the Defense Prisoner of War/ Missing Personnel Office, where she was a senior analyst working to resolve the cases of Americans who remained

unaccounted-for from past conflicts and wars. She left that position after her previous breast cancer (2004) metastasized to her lung in 2006. Shocked to learn how little support and scientific research existed for stage IV cancer, in 2007 CJ established a regional metastatic breast cancer (MBC) support program. It grew rapidly and just 14 months later CJ banded together with 3 other women to found METAvivor Research and Support - the only USA organization exclusively awarding MBC research grants through a scientific peer review process. To date METAvivor has awarded \$1.8 million in MBC research grants.

Julie Gralow, MD

University of Washington School of Medicine
Washington, USA



UW Medicine
SCHOOL OF MEDICINE



Dr. Gralow is the Jill Bennett Endowed Professor of Breast Medical Oncology and Professor of Global Health at the University of Washington School of Medicine and a Member of the Clinical Research Division at the Fred Hutchinson Cancer Research Center. She is Director of Breast Medical Oncology at the Seattle Cancer Care Alliance. She is actively involved in clinical care, education,

and research, and is the PI on numerous local and national clinical trials related to breast cancer treatment, prevention, and survivorship. Her area of research specialization is the relationship between breast cancer and the bone. Dr. Gralow is SWOG Executive Officer for Breast and Lung Cancer. She is currently a member of the American Society of Clinical Oncology's (ASCO) International Affairs Committee, the ASCO Global Oncology Task Force, and the ASCO Breast Cancer Advisory Guideline Group. She received an ASCO Statesman Award in 2008, was elected a Fellow of the American College of Physicians in 2008, and received the Seattle Business Magazine Leaders in Healthcare Achievement in Community Outreach Award in 2014. Dr. Gralow is committed to improving the quality of life for breast cancer patients through education, exercise and diet, and to promoting breast cancer awareness in the community. She is Medical Director and Team Physician for Team Survivor Northwest, aimed at helping female cancer survivors improve their health through fitness and exercise. She is also founder of the Women's Empowerment Cancer Advocacy Network (WE CAN), a group dedicated to empowering women cancer patient advocates in low and middle income countries.



Shirley Mertz

Metastatic Breast Cancer Network
New York City, USA



In 2005, Shirley Mertz began advocating on behalf of others living with metastatic breast cancer through the Metastatic Breast Cancer Network (MBCN), a non-profit, patient-led organization that organizes an annual metastatic breast cancer conference for patients and their caregivers. In 2009, Shirley successfully led a group of patients to Washington D.C. to lobby the U.S. Congress

to pass a resolution declaring October 13 as National Metastatic Breast Cancer Awareness Day. As President of MBCN, Shirley calls for more public understanding of the disease, focused research and helpful information for patients. Shirley is a member of the Executive Committee of the Metastatic Breast Cancer Alliance, the Board of the National Breast Cancer Coalition, and the patient advocate group of the Translational Breast Cancer Research Consortium. A graduate of Project LEAD and a Komen Advocate in Science, Shirley reviews research grants for the DOD Breast Cancer Research Program and Komen. In 2011 the White House honored Shirley as a Champion of Change in Breast Cancer. She has served on the advisory committee for breast cancer patient advocacy for both ABC2 and ABC3.

Musa Mayer

AdvancedBC.org
New York City, USA



Musa Mayer is a 26-year survivor, advocate and author of 3 books on breast cancer. Known for her advocacy on behalf of people living with metastatic disease and their families, her articles on breast cancer and advocacy have appeared in magazines, newsletters, websites and scientific journals. As a research advocate, she serves on steering and data monitoring committees for clinical

trials and patient registries, and on a Department of Defense funded Center of Excellence studying brain metastasis, for which she co-developed BrainMetsBC.org, the only resource of its kind. Her patient surveys have been widely used to improve services. She is a founding member of the Metastatic Breast Cancer Alliance, a broad collaboration of support, research and advocacy organizations and industry partners. Drawing from over a decade of work as a patient representative with the Food and Drug Administration, she broadened her commitment to advocacy education by adding a module on the FDA to her online course: "Understanding Evidence-Based Healthcare: A Foundation for Action," co-developed with epidemiologist Kay Dickersin, Director of the U.S. Cochrane Center at Johns Hopkins Bloomberg School of Public Health. Accessible through US.Cochrane.org, this free course has been completed by thousands of advocates and healthcare workers around the world. Musa's web resource for women with metastatic breast cancer can be found at AdvancedBC.org.



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Diego Paonessa

LIGA ARGENTINA
DE LUCHA CONTRA EL CANCER
Buenos Aires, Argentina



Diego Paonessa is a communications and marketing expert in the corporate and NGO sectors. He is CEO of the Argentina League Against Cancer, as well as an experienced professional with over 18 years being the communications, including the management of the National Department of Social Development for 2 years, 3 years as a director of Communication in SES Foundation and co-founding ADVERTERE advertising agency, where he was the account director for twelve years. He currently collaborates with main international networks in support of health and cancer prevention and care in the world: ALICC, ULACCAM and MOLACAP.

Evi Papadopoulos

Europa Donna Cyprus
Nicosia, Cyprus



Evi Papadopoulos is the President of Europa Donna Cyprus and Vice President of Europa Donna the European Coalition since January 2015. She is a member of the board as well as marketing director of Kean Soft Drinks, Ltd. She has received a BsC in Economics from Brunel University, Uxbridge, UK. She has participated in conferences around the globe, including The World

Conference on Breast Cancer by the American Breast Cancer Coalition Brussels 1997, the Annual Advocacy Training in Milan 2003, All Pan European Europa Donna Conferences, most EBCC conferences, and ABC2 Lisbon 2013. She has participated or organized the European Parliament Brussels 2004 and pink lighting and poster exhibition, lobbying on a national level for National Screening program in Cyprus, informing women of the program and follow up, lobbying for Breast units in Cyprus (press conferences, MME presentations, TV programme appearances, lobbying Ministers and presentations in the Parliament), lobbying for local radiotherapy units, and public speeches to organised groups of women or communities for screening, prevention, their patients' rights, medical liability and the demand for specialized care.



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Fedro Alessandro Peccatori, MD

European School of Oncology

Milan, Italy



Fedro Peccatori is a medical and gynecologic oncologist whose clinical activities mainly include diagnosis and treatment of breast cancer, gynecological malignancies and tumors of young adults. He is Director of the Fertility and Procreation Unit within the Division of Gynecologic Oncology in the Department of Gynecology at the European Institute of Oncology, Milan Italy. His main research projects deal with fertility preservation and counselling in young oncological patients, pharmacological protection of ovarian function during chemotherapy, clinical and molecular characterization of pregnancy associated cancers and research protocols for the treatment of breast and gynaecological malignancies. He has acted as lecturer in a number of international meetings, and in the last 5 years has taught at Varese, Pavia and Milan University. He has been considered eligible within the 2012 Italian call for Associate Professor in Oncology and in Obstetrics and Gynecology. He is Deputy Scientific Director at the European School of Oncology (ESO). As past president of PROFERT he has contributed to build up the Italian network of fertility preservation for cancer patients. In 2012 he has received research grants from the Ministry of Health for a project on cancer and infertility (CCM program) He has acted as referee for European Journal of Chemoprevention, Annals of Oncology, The Breast, International Journal of Gynecologic Cancer, PLOS, Lancet Oncology, Ecancermedicalscience. He is on the editorial committee of Ecancermedicalscience and Cancerworld.

Kimberly Sabelko, PhD

Susan G. Komen

Dallas, USA



As managing director, strategic partnerships & programs, at Susan G. Komen®, Kimberly Sabelko, PhD, works closely with Komen's Scientific Advisory Board, Komen Scholars and Advocates in Science to translate scientific strategy into programs that will have an impact on the lives of breast cancer patients. She is responsible for Komen's strategic partnerships with other non-profit organizations, particularly professional and advocacy organizations focused on breast cancer and/or biomedical research, as well as government agencies such as NCI and FDA and pharmaceutical and biotech companies. She also oversees a portfolio of special grants that respond to unique opportunities to leverage resources across organizations, address critical challenges and cross-cutting issues in research, clinical practice and public health, and/or facilitate the development of infrastructure and tools that will accelerate the translation of scientific discoveries into advances in breast cancer prevention and care. Kim received her PhD in Immunology at Washington University in Saint Louis. Prior to joining Komen in 2010, she was Assistant Director for Special Programs at the American Association for Cancer Research.



Naomi Sakurai

Hope Project NPO
Tokyo, Japan



Naomi Sakurai is the Chief Director of the HOPE project, a non-profit organization established in 2006. She was diagnosed with cancer in the summer of 2004, in her 30's. At that point, she learned to utilize her personal experience with cancer and her social skills to start a support group. This group is currently focusing its efforts on enlightening people and spreading awareness about survivorship. This group appeals to the independent livelihood and self-supporting lifestyles for patients living with the disease and their families. She has presented at the Annual meeting of Japan Society of Clinical Oncology from 2009-2012 and the 72nd Annual Congress of Japan Surgical Association. She has participated in many conferences, including the National Breast Cancer Coalition: Annual Advocacy Training Conference from 2009-2011, being a Project-Lead International in 2009, the 23rd International Breast Cancer Symposium 2010, ASCO Annual Meeting 2010-2012, SABCS 2010-2011, American Association for Cancer Research 2012, and the Survivor and Patient Advocacy Program part of the American Association for Cancer Research 2013. Her breast cancer advocacy engagement includes being a member of The Wellness Community in Japan, Chief Director of the HOPE Project, and member of Cancer Patients Support Organization. She has honors from the Junior Chamber International Japan Director's special award (2007), Avon Products' HELLO TOMORROW Award (2008), Chosen as the Best Survey by Healthcare and Social Policy Program of Tokyo University (2009), and a grant from The Takagi Fund for Citizen Science. She is also a Councilor for the Tokyo Metropolitan Government's City of Welfare project and a member of the National Cancer Center's "Patient/Citizen Panel." She has been a breast cancer survivor since 2004.

Danielle Spence

Breast Cancer Network Australia,
Secondary Breast Cancer Strategy
Camberwell, Australia



Danielle has over 25 years' experience working in the healthcare industry across a range of organizations including public, private and not-for-profit agencies. She has a background in oncology nursing and has managed a number of supportive care projects for women with breast cancer working collaboratively with government, health professionals, consumers and other cancer care stakeholders. She has served on numerous cancer advisory groups and worked in senior policy and advocacy positions in leading cancer organizations. Her current role involves managing a national program to improve information and support for women living with secondary breast cancer.



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Appendices and References



Appendices and References

Introduction References

BRIDGE: Metastatic Breast Cancer Patient Survey. Commissioned by Pfizer. http://mbcn.org/images/uploads/SABCS_BRIDGE_Fact_Sheet2010.pdf. October 13, 2015. (BRIDGE Metastatic Breast Cancer Patient Survey, 2010)

Cancer Experience Registry Index Report 2013-2014. Elevating the Patient Voice. <http://www.cancersupportcommunity.org/MainMenu/ResearchTraining/Elevating-the-Patient-Voice.pdf>. Accessed October 27, 2015. (Cancer Experience Registry Report, 2013-2014)



Appendices and References

Section 1: Appendix 1.1

Patient Perspectives Systematic Literature Search (2/27/2015)

Purpose: The purpose of this search was to better understand patient perspectives in mBC space, particularly regarding patient quality of life, psychological associations, unmet needs in supportive care, and patient treatment preferences and decisions.

Method: For this search, we used a systematic search methodology in order to mitigate the risk of missing relevant content by incorporating all perspectives and by including content from trusted and revered sources.

Sources: In order to gain an understanding of the patient experience, a qualitative literature review was conducted using secondary source data. The search was restricted to the years 2005-2015 in the EMBASE database.

Search Terms: Key search terms were selected with the goal of understanding the patient experience, from diagnosis with mBC to the end-of-life stage. These terms were categorized into 5 topics: disease, subjects, study type, study focus, and exclusion terms. See below for the search strategy.



| Database: EMBASE Publication time period 2005-2015 | | | |
|--|-----------------|---|---|
| Index | Description | Search terms | Hits |
| 1 | Disease area | "metastatic breast cancer" OR ("stage iv" AND "breast cancer") OR "advanced breast cancer" OR "secondary breast cancer" | 15104 |
| 2 | Study subject | "patient" | 3800675 |
| 3 | | ("physician" OR "doctor" OR "oncologist" OR "surgeon" OR "provider") OR "healthcare professional" OR ("nurse") | 963222 |
| 4 | | ("caregiver" OR "care-giver" OR "care giver" OR "carer") OR ("family" OR "spouse") OR ("colleague") | 1066369 |
| 5 | | #2 OR #3 OR #4 | 5080912 |
| 6 | | #1 AND #5 | 9117 |
| 7 | | Study type | "survey" OR "questionnaire" OR "perspective" OR "attitude" OR "perception" OR "satisfaction" OR "opinion" |
| 8 | Study focus | #6 AND #7 | 752 |
| 9 | | "unmet need" OR "support" OR "gap" OR "burden" OR "psychosocial" OR "physical" OR "quality of life" OR "treatment preference" OR "information" OR "decision" OR "treatment satisfaction" OR "communication" | 4139327 |
| 10 | | #8 AND #9 | 491 |
| 11 | Exclusion terms | ("randomize controlled trial" OR "randomized controlled study") | 435392 |
| 12 | | "non metastatic breast cancer" OR "non-metastatic breast cancer" OR "non-metastatic breast cancer" or "early stage" | 481 |
| 13 | | #10 NOT #11 | 454 |
| 14 | | #13 NOT #12 | 407 |
| 15 | | #14 AND "article"/it | 132 |



Section 1: Appendix 1.2

Company-Sponsored Study /Public Study Reports

| Index | Year | Study title | Sponsor |
|-------|------|---|------------------|
| 1 | 2013 | Pan-European Here & Now patient and carer survey | Novartis |
| 2 | 2013 | Patient Perspectives: Communicating With HCPs About Metastatic Breast Cancer | Astra Zeneca |
| 3 | 2013 | Metastatic Breast Cancer in Canada: The lived experience of patients and caregivers | CBCN and RETHINK |
| 4 | 2014 | mBC Alliance Landscape Analysis: Research Report | mBC Alliance |
| 5 | 2014 | Breast Cancer: A Story Half Told | Pfizer |
| 6 | 2014 | Count Us, Know Us, Join Us; Make Your Dialogue Count, (Harris Interactive) | Novartis |

Section 1: Appendix 1.3

Quality-of-Life Instrument Conversion Methodology

Purpose: The purpose of this search was to better understand how quality of life has been measured and reported over time through a systematic literature search.

Method: For this search, we used articles from the systematic search conducted for patient perspectives (see Appendix 1). To better understand how quality of life has been measured and reported over time, 132 studies were reviewed through the literature review. Of these studies, a qualitative analysis was conducted on 14 studies reporting QoL measure values for mBC.

Comparison of QoL in patients with mBC over time required the conversion of all QoL measures to 1 uniform QoL measure using accepted conversion schemes based on published literature (outlined below). EQ-5D was selected as the uniform measure, due to the widespread acceptability. (EuroQol Group, 2004)

After conversion, the following studies were included in the final QoL trend analysis:



Converted Quality of Life Survey Comparison 2004 - 2012

| Study Year | Sample Size | Region | Converted EQ-5D Value | Original QoL Instrument | Method of QoL measurement |
|------------|-------------|-----------|-----------------------|-------------------------|-----------------------------|
| 2004 | 105 | Australia | 0.7201 | EORTC | Cross-sectional survey |
| 2006 | 168 | UK and US | 0.7413 | FACT-B | At baseline of intervention |
| 2006 | 168 | UK and US | 0.7433 | FACT-B | At baseline of intervention |
| 2008 | 36 | US | 0.6990 | FACT-B | At baseline of intervention |
| 2011 | 235 | UK | 0.6914 | FACT-B | Cross-sectional survey |
| 2012 | 21 | Greece | 0.8187 | EORTC | At baseline of intervention |
| 2012 | 21 | Greece | 0.7850 | EORTC | At baseline of intervention |
| 2012 | 169 | US and EU | 0.6367 | FACT-B | Cross-sectional survey |
| 2012 | 191 | US and EU | 0.5890 | FACT-B | Cross-sectional survey |

3 schemes of conversions

1. Convert from EORTC QLQ-C30 to EQ-5D: the conversion from EORTC QLQ-C30 to EQ-5D is based on the study (Kontodimopoulos et al, 2009), this study was selected because the conversion is estimated based on a cohort of Greek population, and the 2 studies that reported EORTC QLQ-C30 values were conducted in Greek and Australia, respectively.
2. Convert from FACT to EQ-5D: the conversion is based on the study (Cheung et al, 2014). There is currently limited study focusing within the breast cancer population and this study was selected because it is the only study focused on breast cancer patients. The conversion scheme based on the "ordinary least square" algorithm is used, as it has the best performance.
3. Convert from SF-12 to EQ-5D: the conversion is based on the study (Lawrence et al, 2004). This study is based on a cohort of the US population, and the conversion scheme with the best performance was selected. Based on data availability in order to convert to EQ-5D values, within all studies that were conducted since 2004, 2 studies are included for EORTC conversion, 4 studies are included for FACT conversion, and 1 study is included for the SF-12 conversion. Values of EQ-5D from studies conducted in the same year were averaged with the sample size as the weight.



Sources: For this review, 14 articles from the Patient Perspectives review were analyzed qualitatively (see Appendix 1.1). Of these articles, 6 were eligible for the quantitative analysis.

Search Terms: See Appendix 1.1 for search terms used.

Results: Of the 14 studies, a variety of quality-of-life measures were utilized: 7 studies reported FACT3 studies reported EQ-5D, 2 studies reported EORTC and 1 study reported SF-12 and hrQoL. Most of the studies that reported QoL values were conducted in developed countries, eg, the US, UK, or, Australia. Recently, studies have also been conducted in Asian, Latin American and African regions; however, adequate QoL values were not reported in the studies reviewed, which limited their inclusion.

Limitations: There are several limitations of the results reported: (1) The patient care literature search is not tailored only for QoL trend analysis, and thus it is possible that the studies that reported QoL are not exhaustive in the analysis; (2) Studies included in the trend analysis are from various countries with different mBC populations. It has been discussed in several studies that the same QoL instrument can have different levels reported in different countries; (3) In addition, the conversion of each instrument to EQ-5D can also potentially introduce bias in the analysis. This is because each conversion scheme is estimated based on a certain population cohort. For example, the FACT to EQ-5D conversion is based on 1 Asian study (Cheung et al, 2014); however, the studies in the literature review are all conducted in the US or the EU. In addition, almost all regression algorithms have estimation errors. These uncertainties should be taken into consideration when interpreting the trend.

| General | Clinical |
|---|---|
| Aranda S, et al. Mapping the quality of life and unmet needs of urban women with metastatic breast cancer. <i>Eur J Cancer Care</i> . 2005;14(3):211-222. | Zhou X, et al. Lapatinib plus capecitabine versus capecitabine alone for HER2+ (ErbB2+)metastatic breast cancer: quality-of-life assessment. <i>Breast Cancer Res Treat</i> . 2009;117(3):577-589. |
| Reed, Elizabeth, et al. Quality of life and experience of care in women with metastatic breast cancer: a cross-sectional survey. <i>J Pain Symptom Manage</i> . 2012;43:747-758. | Abernethy AP, et al. Phase 2 pilot study of Pathfinders: a psychosocial intervention for cancer patients. <i>Support Care Cancer</i> . 2010;18(7):893-898. |
| Gupta S, Zhang J, and Jerusalem, G. The association of chemotherapy versus hormonal therapy and health outcomes among patients with hormone receptor-positive, HER2-negative metastatic breast cancer: experience from the patient perspective. <i>Expert Review of Pharmacoeconomics & Outcomes Research</i> . 2014;14(6):929-940. | Kyrgidis A, et al. Quality of life in breast cancer patients with bisphosphonate-related osteonecrosis of the jaws and patients with head and neck cancer: a comparative study using the EORTC QLQ-C30 and QLQ-HN35 questionnaires. <i>Anticancer Res</i> . 32(8): 3527-3534. |



Section 1: Appendix 1.4

Appropriate Supportive Care while Living with Metastatic Disease Systematic Literature Review

Purpose: The purpose of this search was to better understand the perspectives of patients, physicians, caregivers, and families from patient diagnosis with mBC to final stages of life through a systematic literature search.

Method: For this search, we used a systematic search methodology in order to mitigate the risk of missing relevant content by incorporating all perspectives and by including content from trusted and revered sources.

Source: In order to gain an understanding of patient experience, a qualitative literature review was conducted using secondary source data. The search was restricted to the years 2005-2015, from 3 main databases: EMBASE, Medline, and Cochrane Library.

Search Terms: Search terms were selected with the intent to ascertain all essential articles to understand the patient experience. These terms described types of care or therapies other than standard medical care that may be used from diagnosis of mBC to final stages. A complete list of search terms are provided in the table below.

NB: The terms 'advanced breast cancer' and 'stage IV breast cancer' are not specifically recognized in EMBASE.

| Database: EMBASE Publication time period 2005-2015 | | | |
|--|------------------|---|---------|
| Index | Description | Search terms | Hits |
| 1 | Disease area | mBC/exp OR "mBC" OR "advanced breast cancer" OR "stage IV breast cancer" OR "secondary breast cancer" | 27,823 |
| 2 | | "breast metastasis" | 9,194 |
| 3 | | #1 OR #2 | 27,928 |
| 4 | End-of-life care | "palliative therapy" OR "palliative care" | 85,916 |
| 5 | | "terminal care" | 36,080 |
| 6 | | "supportive care" | 24,878 |
| 7 | | #4 OR #5 OR #6 | 128,585 |
| 8 | | #3 AND #7 | 743 |



Database: MEDLINE Publication time period 2005-2015

| Index | Description | Search terms | Hits |
|-------|------------------|---|--------|
| 1 | | mBC.mp | 22,131 |
| 2 | Disease area | metastatic OR metastasi. mp breast cancer OR tumor OR malignant OR oncology OR carcinoma OR neoplasm OR mas OR growth OR cyst).mp | 32 |
| 3 | | #1 OR #2 | 22,139 |
| 4 | | "advanced breast cancer" or "stage IV breast cancer" or "secondary breast cancer" AND #7 | 284 |
| 5 | | #8 OR #9 | 495 |
| 6 | End-of-life care | "end-of-life" OR "palliative" OR "terminal" OR "supportive" AND "care" | 46,374 |
| 7 | | #3 AND #4 | 489 |
| 8 | | "Palliative Care" OR "Terminal Care" OR "Supportive Care" | 76,565 |
| 9 | | #3 AND #6 | 302 |
| 10 | | #6 OR #7 | 743 |

Database: COCHRANE Publication time period 2005-2015

| Index | Description | Search terms | Hits |
|-------|------------------|---|-------|
| 1 | | MeSH descriptor: (Breast Neoplasms) explode all trees | 8,963 |
| 2 | Disease area | (metastatic or metastasis). mp | 478 |
| 3 | | #1 and #2 | 138 |
| 4 | | MeSH descriptor: (Palliative Care) explode all trees | 1,449 |
| 5 | | MeSH descriptor: (Terminal Care) explode all trees | 378 |
| 6 | End-of-life care | MeSH descriptor: (Supportive Care) explode all trees | 0 |
| 7 | | #4 OR #5 OR #6 | 1,662 |
| 8 | | #3 AND #6 Publication Year from 2005 to 2015 | 0 |



| Database: COCHRANE Publication time period 2005-2015 | | | |
|--|------------------|---|--------|
| Index | Description | Search terms | Hits |
| 1 | Disease area | breast (cancer or tumour OR malignant OR oncology OR carcinoma OR neoplas OR mass OR growth OR cyst).mp | 415 |
| 2 | | (metastatic OR metastasis).mp | 476 |
| 3 | | #1 OR #2 | 188 |
| 6 | End-of-life care | (palliative OR end-of-life or terminal OR supportive).mp AND (care).mp | 12,939 |
| 7 | | #3 AND #4 | 112 |

Source: A total of 1,350 abstracts from these 3 databases were systematically recorded in an Excel document, including relevant source information and abstract text. Of these, 38 abstracts were identified for full review based on relevant themes and content. These articles were fully reviewed and relevant content was highlighted as evidence in this section. Other articles were excluded based on limited access, content being irrelevant to supportive care for mBC patients, or duplication in search results. As this section was not meant to be a systematic literature review report, only the most relevant articles were included. Thorough examination of all abstracts allowed for the best selection of articles relevant to supportive care for patients living with mBC.

Limitations: Despite this systematic approach, limitations to this search methodology exist. Specifically, articles irrelevant for this section might have appeared in the search through selected search terms being used in different contexts. For example, if the search term was “mBC,” non-“mBC” could also appear. To account for this challenge, each abstract was reviewed to determine relevance and inclusion criteria. In addition, there is a potential risk of missing articles if the databases failed to capture all relevant articles in the space based on the search terms used. However, based on the credibility and number of databases, this limitation is unlikely to significantly impact the findings.



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Appendices and References

Section 2: Appendix 2.1

Policy Trends Research Methodology

Purpose: The purpose of this search was to understand global political actions on behalf of patients with mBC.

Method: For this search, a literature scan was conducted to better understand policy trends that may impact the mBC space. Although a formal systematic literature review was not conducted, this section was written based on a thorough search of literature around mBC and policy trends.

Sources: In order to gain an understanding of policy trends, a qualitative literature scan was conducted using secondary source articles. The search was restricted between the years of 2005 and 2015 using the peer reviewed journal *Health Affairs* to find relevant articles. Other supplemental sources were also obtained using PubMed.

Search terms: Search terms were chosen based on their relevance to policy and mBC.

| Category | Key Terms |
|----------|--|
| Disease | "metastatic breast cancer" OR "advanced breast cancer" |
| Category | "policy" |

Results: In *Health Affairs*, the search "metastatic breast cancer' policy" yielded 19 search results. Similarly, "advanced breast cancer' policy" yielded 13 search results. These articles were reviewed for information on cost-effectiveness policy, coverage and reimbursement policy, distinct case studies, and general cancer care. Articles from these searches were fully reviewed for content and relevance, those that were most relevant to mBC policy for the purpose of this report were included in this section. In addition, other articles found from other database or general searches were included in this section to enhance understandings of policies around metastatic and advanced breast cancer.

Limitations: This search was not a systematic literature review and therefore may not scientifically reflect global political decisions on metastatic breast cancer. However, *Health Affairs*, as well as the other peer-reviewed sources used, are trusted sources for gleaning information about global political views in many therapeutic areas and therefore, we believe that this section accurately portrays general policy trends in mBC.



Section 2: Appendix 2.2

Economic Burden Literature Review Methodology (3/17/2015)

Purpose: The purpose of this literature search was to understand the economic challenges mBC patients and their families face from the point of diagnosis until end-of-life.

Method: For this search, we used a systematic search methodology in order to mitigate the risk of missing relevant content by incorporating all perspectives and by including content from trusted and revered sources, particularly that of economic and financial hardships.

Sources: In order to gain an understanding of the economic burden of mBC, a literature review was conducted using secondary source data. The search was restricted between the years of 2005 to 2015 from 4 main databases: Medline, Medline In-Process, EMBASE, and Cochrane Library.

Search terms: Search terms were selected with the intent to ascertain all essential articles related to economic and financial experiences of mBC patients, caregivers, and their families. A complete list of search terms is provided in the table below.

| Category | Key Terms |
|----------|--|
| Disease | "metastatic breast cancer" |
| Category | "economic burden" OR "cost" OR "cost of illness" |

EMBASE search conducted on the 17th March 2015:

| | Searches | Results |
|----|--|---------|
| 1 | "breast"/exp OR breast AND ("metastasis"/exp OR metastasis) | 89,063 |
| 2 | "breast metastasis"/exp OR "breast metastasis" AND [2005-2015]/py | |
| 3 | "breast"/exp OR breast AND ("metastasis"/exp OR metastasis) AND [2005-2015]/py | |
| 4 | #1 OR #2 OR #3 | |
| 10 | economic AND burden | |
| 12 | "cost"/exp OR cost | |
| 13 | #10 OR #12 | |
| 14 | #4 AND #13 | |



MEDLINE search conducted on the 18th March 2015:

| | Searches | Results |
|---|--|---------|
| 1 | Search metastatic breast cancer.mp Filters: published in the last 10 years | 22639 |
| 2 | Search (metastatic OR metastasis).mp breast (cancer OR tumour OR malignan* OR oncology OR carcinoma* OR neoplas* OR mass OR growth* OR cyst).mp; Filters: published in the last 10 years | 29 |
| 3 | #1 OR #2 | 22665 |
| 4 | Search "Cost of Illness"[Majr] Filters: published in the last 10 years | 5021 |
| 5 | #3 AND #4 Published in the last 10 years | 9 |
| 6 | Search ("economic burden") OR "cost" Filters: published in the last 10 years | 175154 |
| 7 | #10 OR #12 | 455 |
| 8 | #5 OR #7 Published in the last 10 years. | 455 |

Cochrane search conducted on the 18th March 2015:

| | Searches | Results |
|---|---|---------|
| 1 | MeSH descriptor: [Breast Neoplasms] explode all trees | 8904 |
| 2 | (metastatic or metastasis).mp | 453 |
| 3 | #1 and #2 | 38 |
| 4 | MeSH descriptor: [Cost of Illness] explode all trees | 1167 |
| 5 | #3 and #4 Publication Year from 2005 to 2015 | 3 |

Cochrane search conducted on the 18th March 2015:

| | Searches | Results |
|---|---|---------|
| 1 | breast (cancer or tumour or malignan* or oncology or carcinoma* or neoplas* or mass or growth* or cyst) .mp | 574 |
| 2 | (metastatic or metastasis) .mp | 453 |
| 3 | #1 and #2 | 179 |
| 4 | (economic or burden or cost).mp | 2207 |
| 5 | #3 and #4 Publication Year from 2005 to 2015 | 93 |



Results: After the searches were completed and duplicates, a total of 526 abstracts were collected and recorded in an excel document, including relevant sources information and abstract text. After reviewing these articles for relevancy, 37 full text articles and 10 abstracts were assessed for eligibility. Articles were removed from the original collection due to differences in language, being therapy specific, demonstrating burden of skeletal events only, not pertaining to mBC, and not portraying cost data. A total of 26 articles and 3 abstracts were included in the quantitative synthesis.

These articles were then fully reviewed to glean key messages and information about the economic challenges of mBC patients. Thorough examination of all articles and abstracts allowed for the best selection of articles relevant to the economic burden piece; however, the writing does include references to other sources to add appropriate context.

Limitations: Despite this systematic approach, limitations to this search methodology exist. Specifically, articles irrelevant for this section might have appeared in the search through selected search terms being used in different contexts. For example, if the search term was “metastatic breast cancer,” non-“metastatic breast cancer” could also appear. To account for this challenge, each abstract was reviewed to determine relevance and inclusion criteria. In addition, there is a potential risk of missing articles if the databases failed to capture all relevant articles in the space based on the search terms used. However, based on the credibility and number of databases, this limitation is unlikely to significantly impact the findings. Lastly, to add necessary context to research findings, articles from separate searches are included in this piece and therefore, for those articles, we cannot be certain that the articles represent all possible perspectives in this space.



Section 2: Appendix 2.3

Public Understanding Literature Search (July 2015)

Purpose: The purpose of this search was to gain an understanding of the public perception of mBC and its potential impact on the patient experience, a literature review was conducted of media and newswire sources.

Method: For this search, we used a systematic search methodology in order to mitigate the risk of missing relevant content by incorporating all perspectives and by including content from trusted and revered sources.

Sources: In order to gain an understanding in the mBC societal experience, a qualitative literature review was conducted using secondary source data restricted between the years of 2005 to 2015 from LexisNexis®.

Search Terms:

| Category | Key Terms |
|-----------|--|
| Therapies | Lapatinib, Trastuzumab OR T, Herceptin, Patritumab, Arimedex OR anastrozole, Aromasin OR exemestane, "aromatase inhibitor", BKM120, BYL719, Paclitaxel OR "Paclitaxel albumin" OR P-A OR Abraxane, Eribulin OR E, Halaven, Bevacizumab OR Bev, LEE011, Abemaciclib, Neratinib, "GnRH agonist", "LHRH agonist", "GnRH antagonist", "LHRH antagonist", Omnitarg, Everolimus OR RAD001 OR EVE OR Afinator, Buparlisib, Entinostat, Fulvestrant OR Falsodex, Femara OR Letrozole, Tamoxifen, Toremifene, Gemzar OR gemcitabine, kadcyla, Pertuzimab OR P, Perjeta, Palbociclib OR PD-0332991 OR IBRANCE OR Ibrance, Vintafolide OR V, Docetaxel, "End of life care" OR "end of life" OR EoL OR "EoL care", "supportive care", "palliative care", "radiation therapy", "CDK 4/6 inhibitor", "surgical therapy", "surgery", "mastectomy" "Lumpectomy", amoxifen, Anthracycline, Capecitabine OR C, Xeloda, "investigational", "radiotherapy", "chemotherapy", "hormone therapy", "endocrine therapy" |
| Disease | MBC OR "metastatic breast cancer", "stage four" OR "stage 4" OR "stage IV", LABC OR "locally advanced breast cancer", ABC OR "advanced breast cancer", HER2+ OR "HER2 positive" OR HER2-positive, HER2- OR "HER2 negative" OR HER2-negative, ER+ OR "estrogen receptor positive", ER- OR "estrogen receptor negative", ER OR "estrogen receptor", "Hormone receptor negative", "Hormone receptor positive", ER+/HER2+ OR HER3+/ER+, ER+/HER2- OR HER2-/ER+, ER-/HER2+ OR HER2+/ER-, "pre menopausal" OR pre-menopausal, premenopausal, "post menopausal" OR post-menopausal, postmenopausal, "secondary breast cancer", TNBC OR "triple negative breast cancer" OR ER-/HER- OR HER2-/ER- |



(continued) **Search Terms:**

| Category | Key Terms |
|--------------------------|---|
| Outcome Measure | OS OR "Overall survival", "survival rate", PFS OR "Progression free survival", "TTP" OR time to progression" |
| Trial | "Phase I" OR "Phase 1" OR P1, "Phase II" OR "Phase 2" OR P2, "Phase III" OR "Phase 3" OR P3, "Phase IV" OR Phase 4" OR P4, "comparative effectiveness" OR "head-to-head" OR "head to head" |
| Metastases | "Brain metastases" OR "central nervous system metastases" OR "nervous system metastases" OR "CNS metastases" OR brain, "Liver metastases" OR Liver, "Skin metastases" OR "Epithelial metastases" OR Skin, "bone metastases" OR bone |
| Patient Reported Outcome | "Patient reported outcomes" OR PRO OR "patient-reported outcomes", Efficacy |
| Tolerability | Tolerance OR Tolerability |
| Side Effects | "adverse effect" OR "adverse effects" OR "adverse reaction" OR "Adverse events" OR AE OR Aes OR PSE OR "Patient safety event" OR "side effects" OR SE OR "adverse reaction" OR "adverse drug reaction" OR "unexpected adverse drug reaction" OR "other adverse event" OR OAE, "drug-drug interaction" OR DDI, toxicity |
| Value | "cost effectiveness" OR "Cost effective," OR "cost-effectiveness," OR "beneficial value" OR "QALY" OR "economic value", "value" OR "risk benefit", Cost, efficiency OR "cost efficiency" |
| Social | discrimination OR prejudice, employment OR fired, insurance OR coverage OR reimbursement OR uninsured OR "employer-sponsored insurance" OR "employer sponsored insurance", "family support" OR support OR family OR burden OR "family impact", "in-home care" OR "in home care" OR "hospital care" OR hospital OR in-patient OR "in patient" OR "hospice care" OR "hospice", prescription OR refill OR medication OR drug, "daily routine" OR lifestyle OR "daily activities", Caregiver, "quality of life" OR QoL OR HRQoL OR "health-related quality of life", Advocacy, Legislation, Awareness, "patient education", "cancer fund", "government aide", "NGO" |
| Country | All country members of the United Nations |



Results: Standard text mining method, TF-IDF approach, was used to assign weight to the word stems identified in each article. All media extractions are tokenized, non-letters removed, and stemmed to reduce complexity. Initial text mining analyses rendered 13,824 word stems covering a broad range of subject areas ranging from treatment to spiritual terms such as “god”. Key word searches were conducted in LexisNexis® and were restricted to the years of 2005-2015 resulting in 998 abstracts. To review the trends of the selected terms, an analysis was performed using a modified version of the “bag-of-words” text mining concept. This method searches for binary outputs of absence or presence by disregarding word order and grammar. To perform this analysis abstract content all punctuation except for +, - and / was replaced with a space and content was scanned using the selected key terms. Results were marked with a “1” or “0” respectively if a term was present or absent.

Limitations: Despite this systematic approach, limitations to this search methodology exist. Specifically, articles irrelevant for this section might have appeared in the search through selected search terms being used in different contexts. For example, if the search term was “metastatic breast cancer,” non-“metastatic breast cancer” could also appear. To account for this challenge, each abstract was reviewed to determine relevance and inclusion criteria. In addition, there is a potential risk of missing articles due the fact that our research was restricted to newspaper articles only.



Section 2: Appendix 2.4

Workplace and Community Literature Review

Purpose: The purpose of this search was to better understand the perspectives of patients, caregivers, and employers from patient diagnosis with mBC to final stages of life through a systematic literature search.

Method: As outlined in more detail below, a broad search strategy was employed to mitigate the risk of missing relevant content by incorporating all perspectives and by including content from trusted and revered sources.

Sources: In order to gain an understanding of patient's societal experience, a qualitative literature review was conducted using secondary source data. Five separate search strategies were used to capture the complete immediate societal impact on the patient. The search was conducted in EMBASE with the search terms listed below.

Search Terms: Search terms were selected with the intent to ascertain all essential articles to understand the patient's societal experience. A complete list of search terms are provided in the table below.

| Category | Search Terms | Number of Articles |
|-------------------------------------|--|--------------------|
| Advanced Cancer and Job Performance | (advance* or metastatic or metastat*) and (cancer* or neoplasm* or tumour* or tumor*) and (("job performance"/ exp or "job performance") or "job satisfaction") | 2 |
| Advanced Cancer and Work and Law | MBC OR "metastatic breast cancer"; "stage four" OR "stage 4" OR "stage IV"; LABC OR "locally advanced breast cancer"; ABC OR "advanced breast cancer"; HER2+ OR "HER2 positive" OR HER2-positive, HER2- OR "HER2 negative" OR HER2-negative, ER+ OR "estrogen receptor positive", ER- OR "estrogen receptor negative", ER OR "estrogen receptor", "Hormone receptor negative", "Hormone receptor positive", ER+/HER2+ OR HER3+/ER+, ER+/HER2- OR HER2-/ER+, ER-/HER2+ OR HER2+/ER-, "pre menopausal" OR pre-menopausal, premenopausal, "post menopausal" OR post-menopausal, postmenopausal, "secondary breast cancer", TNBC OR "triple negative breast cancer" OR ER-/HER- OR HER2-/ER- | 3 |



(continued)

| Category | Search Terms | Number of Articles |
|---|--|--------------------|
| Advanced Cancer and Work | or ("unemployment"/exp or "unemployment") or ("unemployed"/exp or unemployed) or ("retirement"/exp or "retirement") or ("sick leave" or "sickness absence" or "absenteeism") or (vocational* or "work ability" or "work capacity" or "work activity" or "work disability" or "work rehabilitation" or "work status" or "work retention" or "workability" or "employability" or employable or employee) or ("occupation"/exp or "occupation") or ("vocational rehabilitation"/exp or "vocational rehabilitation") or ("work disability"/exp or "work disability") or "disability management") and (advance* or metastatic or metastat*) and (cancer* or neoplasm* or tumour* or tumor*) and (("policy"/exp or policy) or ("support group"/exp or "support group") or support or "policymakers")) and (1997:py or 2004:py or 2005:py or 2006:py or 2007:py or 2008:py or 2009:py or 2010:py or 2011:py or 2012:py or 2013:py or 2014:py or 2015:py) | 18 |
| Advanced Cancer Work and Patient Advocacy | ((("work resumption"/exp or "work resumption") or ("return to work"/exp or "return to work") or ("employment"/exp or "employment") or ("employment status"/exp or "employment status") or ("unemployment"/exp or "unemployment") or ("unemployed"/exp or unemployed) or ("retirement"/exp or "retirement") or ("sick leave" or "sickness absence" or "absenteeism") or (vocational* or "work ability" or "work capacity" or "work activity" or "work disability" or "work rehabilitation" or "work status" or "work retention" or "workability" or "employability" or employable or employee) or ("occupation"/exp or "occupation") or ("vocational rehabilitation"/exp or "vocational rehabilitation") or ("work disability"/exp or "work disability") or "disability management") and (advance* or metastatic or metastat*) and (cancer* or neoplasm* or tumour* or tumor*)) and (advocacy or ("patient advocacy"/exp or "patient advocacy")) | 3 |
| mBC and the Wider Community | (((((advance* near/6 breast and ("cancer"/exp or cancer) or (advance* near/6 breast and ("neoplasm"/exp or "neoplasm")) or (advance* near/6 breast and carcinoma*) or (advance* near/6 breast and tumour*) or (advance* near/6 breast and tumor*) or (metastatic near/6 breast and ("cancer"/exp or cancer)) or (metastatic near/6 breast and ("neoplasm"/exp or "neoplasm")) or (metastatic near/6 breast and carcinoma*) or (metastatic near/6 breast and tumour*) or (metastatic near/6 breast and tumor*)) and (((("social environment"/exp or "social environment") or ("support group"/exp or "support group") or ("social isolation"/exp or "social isolation") or "community support" or "community attitude" or ("social support"/exp or "social support") or ("friend"/exp or "friend") or ("peer group"/exp or "peer group")) or "public awareness")) not "early stage") and (2004:py or 2005:py or 2006:py or 2007:py or 2008:py or 2009:py or 2010:py or 2011:py or 2012:py or 2013:py or 2014:py or 2015:py) | 11 |



Results: A total of 37 articles were systematically recorded in an Excel document, including relevant source information and abstract text. These articles were fully reviewed and relevant content was highlighted as evidence in this section. Reasons for article exclusion included content being irrelevant for mBC patients or duplication in search results. As this section was not meant to be a systematic literature review, only the most relevant articles were included. Thorough examination of all abstracts allowed for the best selection of articles relevant to supportive care for patients living with mBC.

Limitations: Despite this systematic approach, limitations to this search methodology exist. Specifically, articles irrelevant for this section might have appeared in the search through selected search terms being used in different contexts. For example, if the search term was “mBC,” non-“mBC” could also appear. To account for this challenge, each abstract was reviewed to determine relevance and inclusion criteria. In addition, there is a potential risk of missing articles if the databases failed to capture all relevant articles in the space based on the search terms used. However, based on the credibility and number of databases, this limitation is unlikely to significantly impact the findings.

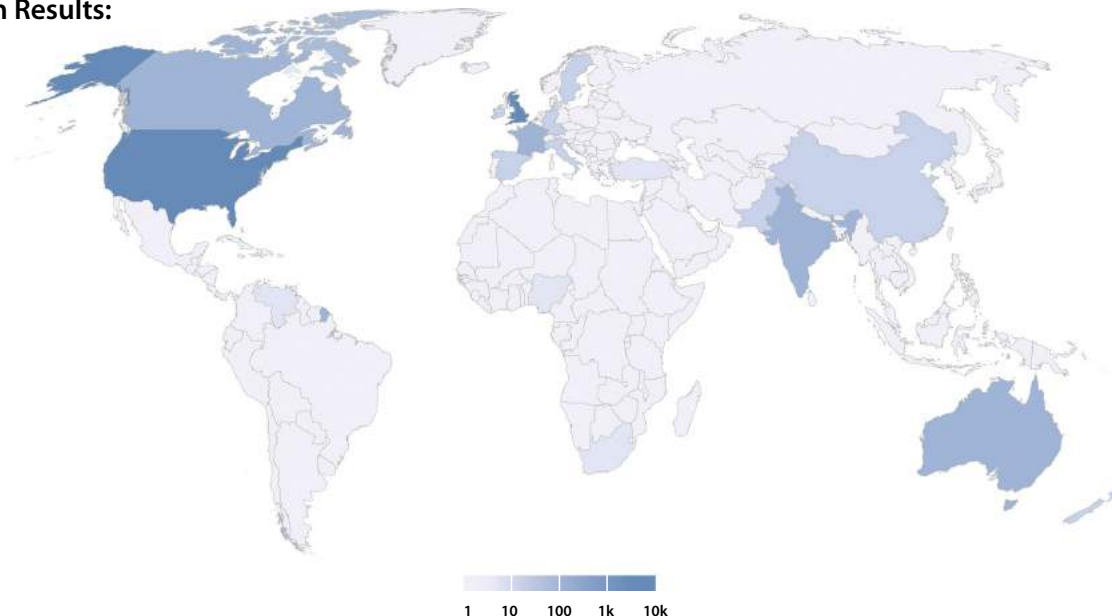


Section 2: Appendix 2.5

Online Media 90 Day Snapshot Methodology

To capture the online media environment for patients with mBC, a 90 day snapshot of media sites was analyzed through the LexisNexis® Newsdesk tool from September 7 through December 16, 2015. This tool monitors media from print news, online news, broadcasts, and social media sources from around the world, with the aim of understanding the current landscape around a certain organization or topic. Search terms were entered into the LexisNexis® system to reveal 113 media clips related to mBC. Of these, the perceptions varied greatly: 1 mixed, 1 neutral/positive, 39 positive, 17 negative, 1 neutral/negative, 54 neutral. The search terms used in the system were “metastatic breast cancer” OR “advanced breast cancer” OR “Stage IV breast cancer” OR “Stage 4 breast cancer” AND “mbc” AND “cancer”. Findings from this search were included in this chapter.

Map of LexisNexis® Search Results:



A breakdown of how many references came from each site and from where in the world are listed below.

| Site | Number of Hits |
|---------------------|----------------|
| Facebook | 70 |
| Reddit | 30 |
| The New Yorker | 1 |
| Buzzfeed | 2 |
| The Washington Post | 1 |
| Google Plus | 1 |
| Twitter | 15 |
| The Guardian | 2 |



Section 2: References

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Appendices and References

Section 3: Appendix 3.1

Scientific Landscape Literature Search Methodology

Purpose: The purpose of this literature search was to better understand the scientific landscape for mBC patients, with specific focus on research and treatment advancements.

Method: For this search, we used a systematic search methodology to mitigate the risk of missing relevant content, by incorporating all perspectives, and by including content from trusted and revered sources.

Sources: To gain an understanding of the scientific landscape for mBC, a qualitative literature review was conducted using secondary source data from the EMBASE database, published from 2004 to 2015.

Search Terms: Search terms were selected with the intent to ascertain all essential articles. These terms described treatments, therapies, clinical trial research, survival outcomes, quality of life, treatment satisfaction, and patient burden. A complete list of search terms is provided in the table below.

Search Terms Used Within EMBASE

| Category | Key Terms |
|------------------|--|
| Disease | "mBC" OR "stage IV breast cancer" OR "advanced breast cancer" OR "secondary breast cancer" |
| Study Type | "randomized controlled trial" OR "randomised controlled trial" OR "randomized controlled trials" OR "randomised controlled trials" |
| Clinical Outcome | "progression free survival" OR "median progression free survival" OR "median pfs" AND "overall survival" OR "median overall survival" OR "median os" |
| Publication Date | 2004 to 2015 |



Results: A total of 267 studies from EMBASE were systematically recorded in an Excel document, including relevant source information and abstract text. For clarity, results were categorized as a clinical-trial study or a meta-analysis of clinical studies. Of these, 72 studies were identified for full journal article review, based on relevant themes and content. Thorough examination of all abstracts allowed for the best selection of articles relevant to scientific changes and data in mBC. Some articles were excluded based on limited access, content being irrelevant to the scientific landscape for mBC, or duplication in search results. The remaining articles were used to inform the writing of the scientific landscape section; however, the writing does include references to other sources to add appropriate context.

Limitations: Despite the systematic approach, there are limitations to this search methodology. Specifically, articles irrelevant for this section may have appeared in the search through selected search terms being used in different contexts. For example, if the search term was “mBC,” non-“mBC” could also appear. To account for this challenge, each abstract was reviewed against inclusion criteria to determine relevance. In addition, there is a potential risk of missing articles if the databases failed to capture all relevant articles in the space based on the search terms used. However, based on the credibility and number of databases, this limitation is unlikely to significantly impact the findings. Lastly, to add necessary context to research findings, articles from separate searches are included. We cannot guarantee those articles represent all perspectives.



Section 3: Appendix 3.2

Medical Conference Abstract Research Methodology

Purpose: The purpose of this conference review research was to understand the major points of discussion and scientific change in the mBC field.

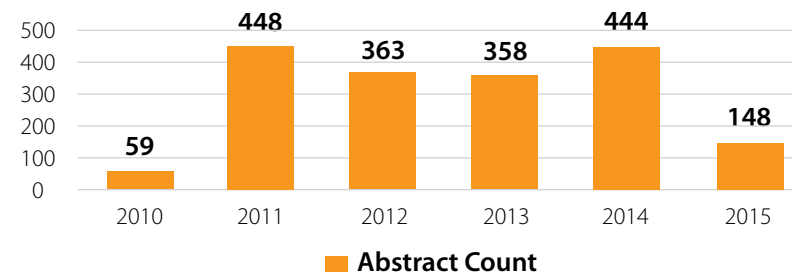
Method: A text-mining search was conducted with abstracts gathered from conferences covering mBC. This method searches for binary outputs of absence or presence by disregarding word order and grammar. To perform this analysis, all punctuation except for +, - and / was replaced with a space and content was scanned using the 408 key terms. Results were marked with a "1" or "0", respectively, if a term was present or absent. Results were grouped based on synonym relationships to one another (ie, end-of-life care and EOL). A proper percentage was used to account for yearly variation in publication numbers and reduce potential bias in the analyses.

Sources: Abstracts from conferences held from 2010 to 2015 were collected from relevant organization Web sites, including the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), European Cancer Congress (ECCO), Impacting Care and Knowledge Through Translational Research in Breast Cancer (IMPAKT), hosted by ESMO and the Breast International Group (BIG), the San Antonio Breast Cancer Symposium, (SABCS), and the Advanced Breast Cancer International Consensus Conference (ABC). Each organization has links directly to abstracts featured at each conference, which were utilized to conduct this search.

Search Terms: Four separate searches were performed within these conference sites using the terms "mBC," "secondary breast cancer," "advanced breast cancer," and "stage four."

Results: To review the trends for the selected terms, an analysis was performed using a modified version of the "bag-of-words" text-mining concept. The resulting 1820 abstracts were systematically recorded in Excel, including their titles, affiliations, and text. A breakdown of abstracts by year is shown in the figure below.

Figure: Abstracts Collected From ASCO, IMPAKT, SABCS, ABC, and ESMO During 2010-2015 (Note: 2015 consists of data through ASCO 2015).



Content and titles were reviewed to identify key terms (N=283); terms were included based on perceived relevance to the content. The list was reviewed and extrapolated to include potential synonyms by 2 senior team members, resulting in a final total of 408 abstracts.

Limitations: Limitations for this method of research derive from the manual work done to collect the abstracts. Whilst each organization's conference was systematically researched, some abstracts could have been missed due to the nature of the operation. However, because this analysis was based on common terms, the few abstracts missed likely would not have a significant impact on results.



Section 3: Appendix 3.3

mBC Phase II and III Clinical Trials by Subtype

Purpose: The purpose of this review of ClinicalTrials.gov was to identify Phase III clinical trials for investigational targeted agents, by subtype and class of agent, that have not yet been approved for the treatment of patients with mBC.

Method: ClinicalTrials.gov was accessed on September 15, 2015, and a search was conducted to identify the number of investigational targeted agents in each therapeutic class for the treatment of mBC subtypes. Investigational targeted agents were defined as those that have not been approved for breast cancer at a cut-off date of December 2014, and for which there were only open Phase III trials from which data are awaited, or are positive. Trials for chemotherapeutic agents were excluded, as were trials exploring different dosages and/or regimens of FDA-approved therapies.

Trials were also identified by subtype and classified as HR+/HER2-mBC trials, HER2+ mBC trials, or TNBC mBC trials. A selection of large (>100 patients), randomized, Phase II trials evaluating novel investigational agents in TNBC was also identified.

Sources: Clinicaltrials.gov accessed on September 15, 2015.

Search Terms: Phase II or Phase III trials, interventional, search terms included “mBC,” “secondary breast cancer,” “advanced breast cancer,” and “stage four.”

Results: The resulting 21 Phase III clinical trials were systematically recorded in Excel, including subtype, clinical trial identification number, trial name, and class. The breakdown of Phase III clinical trials by subtype is shown in the table below.



| Open Phase III mBC Clinical Trials by Subtype | | | |
|---|----------------------------|------------------|----------|
| Subtype | NCT # | Trial name | Class |
| HR+/HER2- | NCT01610284 | BELLE 2 | PI3K |
| | NCT01633060 | BELLE 3 | PI3K |
| | NCT01958021 | MONALEESA 2 | CDK |
| | NCT02422615 | MONALEESA 3 | CDK |
| | NCT02278120 | MONALEESA 7 | CDK |
| | NCT02107703 | MONARCH 2 | CDK |
| | NCT02246621 | MONARCH 3 | CDK |
| | NCT01740427 | PALOMA 2 | CDK |
| | NCT01942135 | PALOMA 3 | CDK |
| | NCT02028507 | PEARL | CDK |
| | NCT02340221 | SANDPIPER | PI3K |
| | NCT02437318 | SOLAR 1 | PI3K |
| | NCT02115282 | - | HDAC |
| HER2+ | NCT02213744 (Phase II/III) | HERMIONE | Biologic |
| | NCT01808573 | NALA | TKI |
| | NCT02492711 | SOPHIA | Biologic |
| TNBC | NCT01905592 | BRAVO or BIG5-13 | PARP |
| | NCT02163694 | BROCADE | PARP |
| | NCT01945775 | EMBRACA | PARP |
| | NCT02000622 | OlympiAD | PARP |
| | NCT02425891 | - | PD-L1 |

Limitations: Limitations for this method of research derive from the manual work done to collect the clinical trials. While ClinicalTrials.gov was systematically researched, some trials could have been missed, due to the nature of the operation.



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Primary Research Appendices: Breast Cancer Center Survey

Pfizer Commissioned Survey

Purpose: This survey was fielded with the aim of understanding the role of breast cancer centers in the management and support of mBC patients. It revealed HCP perceptions of mBC patients' needs as well as determined the types of psychosocial, informational support, and counseling provided to mBC patients and their caregivers. The survey also

identified key channels of communication and resources used to educate and inform mBC patients and HCPs.

Method: The survey was fielded between July 21 and August 26, 2015 to a total of 582* Healthcare Professionals (HCPs) across 9 countries. The table below shows the breakdown of interviewees within each country:

| Country | Physician (n=336) | Nurse (n=207) | Leader (n=39) | Total (n=582) |
|-----------|-------------------|---------------|---------------|---------------|
| USA | 103 | 50 | 19 | 172 |
| Australia | 18 | 14 | 0 | 32 |
| Germany | 29 | 25 | 3 | 57 |
| UK | 41 | 24 | 6 | 71 |
| Italy | 67 | 24 | 4 | 95 |
| Portugal | 22 | 25 | 3 | 50 |
| Brazil | 23 | 21 | 1 | 45 |
| Mexico | 24 | 20 | 2 | 46 |
| *Sweden | 9 | 4 | 1 | 14 |

* Because of the small sample collected in Sweden (n=14), results are analyzed separately and included in open-end reporting only



Respondents self-administered a 30 minute double-blinded survey over the Internet. The Steering Committee members had an integral role in shaping the scope and content of the survey. Definitions for specific

terms were shown initially and then made available each time these words/phrases appeared. Terms included: palliative care, end-of-life care, and hospice. Definitions are shown below:

| | |
|------------------|---|
| Palliative Care | <p>This is also referred to as “supportive care” or “symptom management”.</p> <p>Defined as care provided across the patient journey that aims to improve the quality of life of patients suffering life-threatening illness, and its impact on their families, through the prevention and relief of the symptoms of a disease, side effects caused by treatment of a disease, and psychological, social, and spiritual problems related to the disease or its treatment.</p> <p>When referring to palliative care, this does not mean end-of-life or hospice care. (National Cancer Institute and World Health Organization)</p> |
| End-of-Life Care | <p>Providing care for people in the last phases of an incurable disease so that they may live as fully and comfortably as possible. (American Cancer Society)</p> |
| Hospice | <p>This is also referred to as “end-of-life care”.</p> <p>A program that provides special care for people who are near the end-of-life and for their families, either at home, in freestanding facilities, or within hospitals. (American Cancer Society)</p> |

Respondents Profile: Physician specialties included those in medical/clinical oncology and in Germany a small sample of gynecologists. All nurses were oncological nurses, and leaders included C-level officers, administrators, or medical directors of oncology programs at the center. All interviewees were selected based on specific criteria to ensure consistency across countries and centers as well as involvement with mBC patients.

About 50% of respondents came from institutions with an accredited breast cancer program (ie, accredited by the National Accreditation for Breast Cancer (NAPBC), American College of Surgeons, and/or the European Society of Breast Cancer Specialists (EUSOMA)).

The table below summarizes locations and setting of practice across all respondents:

| | |
|----------|---|
| Location | <p>77% Urban</p> <p>19% Suburban</p> <p>4% Rural</p> |
| Setting | <p>35% Academic</p> <p>22% Public</p> <p>19% Specialty</p> <p>17% Community</p> <p>7% Private</p> |



The table below summarizes key metrics on the average center sizes across all respondents:

| | |
|---|-----|
| Average Number of Full-time Physician Treaters involved in Management/Treatment of BC | 12 |
| Average Number of Outpatient/Day Hospital Infusion Chairs/Beds for BC Patients | 18 |
| Average Number of Inpatient Infusion Chairs/Beds for BC Patients | 13 |
| Average Number of Cancer Patients (past 3 months) | 239 |
| Average Number of mBC (past 3 months) | 50 |

Results: The Global Status of mBC Decade Report contains the detailed and key findings from this survey.

Limitation: Results were based on respondent recall and perceptions.



Primary Research Appendices: mBC General Population Survey

Pfizer Commissioned Survey

Purpose: The purpose for conducting this survey was to determine the general public's awareness and knowledge of advanced/metastatic breast cancer relative to breast cancer overall, particularly in terms of disease impact, prognosis, availability of treatments, and expectations for what treatment can accomplish.

Method: Between June 3 and July 30, 2015, a total of 14,315 adults were surveyed in 14 countries. The adult general public was sampled using Internet research panels and face-to-face intercepts, and

invited to complete a 15-minute questionnaire. Data were weighted to key demographic parameters within each country to ensure representativeness of the population. A breakdown of these countries is shown below.

Data were collected through online self-administration or face-to-face interviews using a double-blinded survey developed with input from the Steering Committee, who had an integral role in shaping the scope and content of the survey:

| Country | Number | Online Sample* | Data Collection |
|--------------|--------|----------------|--------------------------|
| UK | 1,001 | GP | Online Self-Administered |
| France | 1,001 | GP | Online Self-Administered |
| Germany | 1,011 | GP | Online Self-Administered |
| Poland | 1,000 | OP | Online Self-Administered |
| Turkey | 1,009 | OP | Online Self-Administered |
| India | 1,045 | OP | Online Self-Administered |
| Taiwan | 1,001 | OP | Online Self-Administered |
| Japan | 1,000 | GP | Online Self-Administered |
| South Africa | 1,039 | OP | Online Self-Administered |
| Brazil | 1,196 | OP | Online Self-Administered |
| Mexico | 1,003 | OP | Online Self-Administered |
| Argentina | 1,007 | GP | Online & Face-to-Face |
| Chile | 1,002 | GP | Online & Face-to-Face |
| Colombia | 1,000 | GP | Online & Face-to-Face |

*GP = General population of adults, 18+; OP = "Online population" (typically skews to younger, better educated, more urban adults)



Respondent profile: About half of the survey respondents in each country were women, with the exception of Turkey and India, where women accounted for smaller proportions of the samples. The majority of respondents in Turkey, India, Taiwan, Brazil, and Mexico report having received at least some university education (52%-82%). The majority of respondents in all countries (51%-70%) except Taiwan (20%) and Japan (22%) reported they have known someone with breast cancer, but few in any country have been diagnosed themselves (1%-8%).

Results: The Global Status of mBC Decade Report contains the detailed and key findings from this survey.

Limitations: The survey is not designed to support either a global total or regional totals on a representative basis (because sample sizes in the 14 countries are similar notwithstanding different population sizes). Due to

differences in method and representativeness described above, direct comparisons between countries should be made cautiously. In countries with high-internet penetration rates and well-developed online research panels, such as the UK, France, Germany and Japan, online panel data may be viewed as representative of the general adult population. However, in countries with lower Internet penetration or where Internet research panels are relatively under-developed, such as Poland, Turkey, India, Taiwan, South Africa, Brazil and Mexico, the data are representative of the online population of adults, which may be younger and more educated than those without Internet access. Because a mixed-mode approach (ie, Internet panels and face-to-face intercepts) was used in Argentina, Chile, and Colombia, the samples in these countries may be viewed as providing approximate representation of the general adult population.



Primary Research Appendices: Patient Support Organization Qualitative Survey

Pfizer Commissioned Survey

Purpose: The purpose of this qualitative primary research among breast cancer patient support organizations (PSOs) included: understanding PSO goals and perceived needs of breast cancer patients, especially mBC patients, developing a landscape of activities provided by PSOs, identifying challenges PSOs face in advancing priorities, and understanding any opportunities in leveraging resources.

Method: Between June 15 and August 3, 2015, a total of 50 in-depth interviews were conducted with key members of PSOs that focus on mBC, BC, and/or cancer in 28 countries across 5 regions. Individuals

interviewed had strategic and/or program responsibilities. Specifically, respondents needed to be moderately or highly involved in directing, developing and/or managing health education, outreach, evaluation and/or outcomes for their organization. The research was single blinded as Pfizer was revealed as the study sponsor, but identities of respondents and organizations remained blinded.

Each interview was 45-60 minutes in length, with most completed via telephone. The table below shows the breakdown of respondents by country/region:

| | US and Canada (US/CA) | Europe (EU) | Asia Pacific (including Australia) (APAC) | Latin America (LA) | Africa and Middle East (AfME) |
|-------------|-----------------------|---|--|---|--|
| Respondents | 11 | 14 | 7 | 10 | 8 |
| Countries | Canada US | Belgium France Germany Greece Ireland Italy Poland Spain Turkey United Kingdom | Australia China Japan South Korea | Argentina Brazil Colombia Costa Rica Dominican Republic Mexico | Egypt Kenya Rwanda Saudi Arabia Uganda Zambia |



A comprehensive discussion guide was developed with the guidance of the Steering Committee, who had an integral role in shaping the scope and content of the discussion guide. Given the qualitative nature

of the research, however, each discussion was driven by the interests, knowledge, and expertise of respondents.

Respondent Profile: Below is a description of each PSO interviewed by reach, size, focus, and the number of activities* offered:

| Reach | | | | | Size | | | (Aided) Number of Activities for BC Patients | Cancers Supported | | Region |
|----------------|----------|-------------|----------------|------|----------|-------|---------|---|-------------------|--------------------------|--------|
| Multi-National | National | Multi-State | State/Province | City | Under 30 | 30-70 | Over 70 | | BC Only | BC Plus Other Cancers | |
| X | | | | | | | X | 11 | | X | EU |
| X | | | | | | | X | 8 | X | | LA |
| X | | | | | | | X | 12 | | X | AfME |
| X | | | | | | | X | 8 | X | | EU |
| X | | | | | X | | | 10 | | X | EU |
| X | | | | | X | | | 11 | | X | EU |
| X | | | | | X | | | 8 | | X | LA |
| X | | | | | X | | | 12 | X | | AfME |
| | X | | | | | | X | 13 | | X | EU |
| | X | | | | | | X | 11 | | X | US/CA |
| | X | | | | | | X | 10 | | X | EU |
| | X | | | | | | X | 9 | | X | US/CA |
| | X | | | | | | X | 6 | | X | EU |
| | X | | | | | | X | 4 | | X | APAC |
| | X | | | | | | X | 12 | X | | US/CA |
| | X | | | | | | X | 8 | X | | LA |
| | X | | | | | | X | 14 | | X | US/CA |
| | X | | | | | | X | 10 | | X | AfME |
| | X | | | | | | X | 10 | | X | EU |
| | X | | | | | | X | 12 | X | | AfME |
| | X | | | | | | X | 11 | X | | EU |
| | X | | | | | | X | 10 | X | | EU |



(continued)

| Reach | | | | | Size | | | (Aided) Number of Activities for BC Patients | Cancers Supported | | Region |
|----------------|----------|-------------|-----------------|------|----------|-------|---------|---|-------------------|--------------------------|--------|
| Multi-National | National | Multi-State | State/ Province | City | Under 30 | 30-70 | Over 70 | | BC Only | BC Plus Other Cancers | |
| | X | | | | | X | | 9 | X | | AfME |
| | X | | | | | X | | 7 | X | | US/CA |
| | X | | | | X | | | 11 | | X | LA |
| | X | | | | X | | | 11 | | X | EU |
| | X | | | | X | | | 10 | | X | US/CA |
| | X | | | | X | | | 9 | | X | AfME |
| | X | | | | X | | | 7 | | X | AfME |
| | X | | | | X | | | 13 | X | | AfME |
| | X | | | | X | | | 9 | X | | US/CA |
| | X | | | | X | | | 7 | X | | LA |
| | X | | | | X | | | 7 | X | | APAC |
| | X | | | | | n/a | | 11 | X | | EU |
| | | X | | | | | X | 7 | X | | US/CA |
| | | X | | | | | X | 13 | X | | LA |
| | | X | | | | X | | 8 | X | | EU |
| | | X | | | X | | | 6 | X | | US/CA |
| | | | X | | | | X | 10 | X | | US/CA |
| | | | X | | | X | | 12 | X | | US/CA |
| | | | X | | | X | | 11 | X | | LA |
| | | | X | | | X | | 6 | X | | LA |
| | | | | | | | | 5 | | | APAC |
| | | | | | | | | 9 | | | APAC |
| | | | | | | | | 12 | | | APAC |



(continued)

| Reach | | | | | Size | | | (Aided) Number of Activities for BC Patients | Cancers Supported | | Region |
|----------------|----------|-------------|-----------------|------|----------|-------|---------|---|-------------------|--------------------------|--------|
| Multi-National | National | Multi-State | State/ Province | City | Under 30 | 30-70 | Over 70 | | BC Only | BC Plus Other Cancers | |
| | | | | X | | | X | 5 | | X | AfME |
| | | | | X | | | X | 9 | X | | APAC |
| | | | | X | | X | | 12 | X | | EU |
| | | | | X | X | | | 11 | | X | LA |
| | | | | X | X | | | 9 | | X | LA |
| | | | | X | X | | | 7 | | X | APAC |
| | | | | X | X | | | 6 | X | | APAC |
| | | | | X | X | | | 6 | X | | APAC |

*Written descriptions of 14 activities were provided during the interview and respondents were asked to identify the activities they offer in support of BC patients

The number of activities offered does not appear to correlate with the size or reach of organization. The tables below can only be interpreted at a directional level because of the small sample size.

| | Size | | |
|-------------------------|----------|-------|---------|
| | Under 30 | 30-70 | Over 70 |
| #PSOs | 19 | 15 | 15 |
| Average # of Activities | 9 | 10 | 9 |

| | Reach | | | | |
|-------------------------|----------------|----------|-------------|-----------------|------|
| | Multi-National | National | Multi-State | State/ Province | City |
| #PSOs | 8 | 26 | 4 | 4 | 8 |
| Average # of Activities | 10 | 10 | 9 | 10 | 8 |

Results: Detailed and key findings are shown in the Global Status of mBC Decade Report (particularly in Section 2, Chapter 4: *The Impact of Patient Support and Advocacy Organizations in mBC*).

Limitations: While these interviews revealed the perceived needs of mBC patients as well as support provided by PSOs, the findings reflect opinions

of a small number of key members from global PSOs. Analyses should be evaluated in context of other secondary and primary research data. All tallies presented aim to be accurate but without claiming any statistical relationship or significance.



Primary Research Appendices: mBC Patient and Caregiver Qualitative Research

Pfizer Commissioned Survey

Purpose: The objective of this research was to assess the experiences of patients and caregivers affected by mBC. This qualitative research specifically explored the personal perspectives of mBC patients and caregivers, including their own perceptions of the community's opinions on mBC, the impact of these perceptions on the patient, and the interactions between the patients and the community. Caregivers provided their perceptions of the mBC patient's experience along the disease progression and described their role in support and caregiving.

Method: One-on-one interviews were conducted between January 6-29, 2016 among a total of 28 mBC patients and caregivers in 7 countries, of which three pairs of patients and their caregivers were interviewed. Interviews were conducted either over the phone or face-to-face for 60 minutes and were double-blinded. The table below shows the breakdown of respondents by country:

| Country | mBC Patients | Caregivers | Interview Approach |
|---------|--------------|------------|--------------------|
| US | 2 | 2 | telephone |
| UK | 2 | 2 | telephone |
| Turkey | 2 | 2 | telephone |
| India | 2 | 2 | face-to-face |
| Egypt | 2 | 2 | face-to-face |
| Brazil | 2 | 2 | telephone |
| Mexico | 2 | 2 | telephone |
| Total | 14 | 14 | |

Other large studies of patient experience have been conducted including the BRIDGE survey and MBC Alliance Landscape Analysis. Those findings should also be considered when evaluating patient experience.



Respondent profile: Of the patients interviewed, approximately 50% had been diagnosed as de novo mBC and approximately 50% had progressed from eBC. Patients were diagnosed anywhere between the prior 6 months to 10 years. A majority of these patients were HR+ and there was approximately an equal split of patients that were HER2+ and HER2-, with one patient having TNBC. The age range of patients interviewed varied, as per the table below.

| Age | Number of Patients |
|-------------|--------------------|
| 30-39 years | 4 |
| 40-49 years | 5 |
| 50-59 years | 3 |
| 60-69 years | 2 |
| Total | 14 |

Of the 14 patients and 14 caregivers interviewed, 21 of the patients that were subjects of the interviews were unemployed. Caregivers identified themselves as daughters, sons, or husbands of the mBC patients who spend at least 15 hours a week caregiving. Three of the patients interviewed for this report also had their caregiver interviewed. One of the respondents interviewed provided the perspective of a caregiver whose loved one with mBC had passed away.

Results: The Global Status of mBC Decade Report contains the details and key findings from this research.

Limitations: Results were based on respondent recall and perceptions. In addition, the findings reflect the opinions of a small number of mBC patients and caregivers and therefore should be considered as directional.



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