

Global Status of Advanced / Metastatic Breast Cancer

2005-2015 Decade Report

Summary



INTRODUCTION

Breast cancer (BC) represents a significant public health burden across the globe. Over the last decade, substantial resources directed toward BC education, research, and advocacy efforts have led to gains in detection, treatment, and outcomes. Yet, these efforts have mainly benefited those with early breast cancer (eBC). As a result, the need for support and treatment for people living with advanced or metastatic BC has been left in the shadows. The *Global Status of Advanced/Metastatic Breast Cancer 2005-2015 Decade Report* is a comprehensive analysis of the metastatic breast cancer (mBC) landscape over the past decade. It reveals areas of improvement as well as substantial gaps in care, access to resources and support, and treatment outcomes for patients with mBC, which is widely considered incurable. Highlighting the improvements and reinforcing the gaps and challenges that persist is an important step to rally the global BC community to improve the care and treatment of people with mBC.

This report builds on 2 important initiatives from the last decade that illuminated the significantly different needs and experiences of patients with mBC, the most advanced stage of breast cancer. The global BRIDGE survey, published in 2010, and the 2014 MBC Alliance Landscape Analysis in the US, recognize that mBC management and support has improved over the last decade; however, significant gaps still remain. Taken together, these 2 reports shed light on the mBC landscape as compared with eBC in the US and other countries and inspired the development of the *Global Status of mBC Decade Report* to further explore mBC on a worldwide scale.

At the initiation of this report much remained unknown, but one thing was clear – there is an urgent need for change in mBC. Almost all of the more than half a million BC deaths around the world each year are due to metastatic disease (GLOBOCAN, 2012; Lu, 2009) and while survival varies by subtype and by patient characteristics, the median survival rate of 2-3 years for mBC has not changed significantly in decades (NCI SEER, 2015; Weide, 2014; Lobbezoo, 2013).

Broadly, the *Global Status of mBC Decade Report* finds that:

- There is a lack of public knowledge about mBC compared with eBC that leads to widespread misperceptions.
- Access to supportive and palliative care is not yet globally achieved.

GLOBAL mBC FACTS AND FIGURES

- mBC is the most advanced stage of BC, where the cancer has spread from the breast to other parts of the body
- 1.7 million new cases of BC were diagnosed in 2012 worldwide (IARC, Breast Cancer, 2015; Lu, 2009)
- 5-10% of patients are diagnosed at the metastatic stage of the disease (Cardoso, 2012) with as many as 50-80% in developing countries (Unger-Saldana, 2014)
- While data are lacking, some studies have found that approximately 20-30% of eBC patients may recur with mBC (O'Shaughnessy, 2005; EBCTCG, 2015)
- Median survival for mBC is 2-3 years (NCI SEER, 2015; Weide, 2014; Lobbezoo, 2013)
- It is estimated that 561,334 BC deaths occurred worldwide in 2015, primarily from mBC. By 2030, the number of deaths is estimated to reach 805,116, representing a 43% increase in absolute number of BC deaths. (WHO, 2013)

- A greater focus on mBC-specific patient support and advocacy is needed to help patient support organizations (PSOs) overcome barriers to implementing mBC-specific support and resources.
- Patient and physician communication needs to be improved.
- Scientific advances for mBC have not kept pace with those for other cancers.

The goal of this report is to shed light on the challenges and gaps in mBC to inspire worldwide change within the BC community and beyond, including physicians, researchers, policymakers, industry, advocates, caregivers, patients, and the public. It is one of the most far-reaching analyses of the key factors that contribute to the care and well-being of those with mBC and provide insight on areas in need of improvement.

To read the **full report**, please visit www.BreastCancerVision.com.

THE REPORT

The *Global Status of mBC Decade Report* is the first globally focused assessment of advanced/metastatic BC across the care continuum, as well as the political, societal, and scientific landscapes. It was developed by Pfizer Oncology, working collaboratively with the European School of Oncology (ESO) within the scope of the Advanced Breast

Cancer Third International Consensus Conference (ABC3). A global, multidisciplinary steering committee comprised of physicians, patient support organization leaders, and patients advised and contributed to the report (see page 3).

The report covers 3 core areas:



SECTION 1: **PATIENT CARE PERSPECTIVES**

Examines information and communication needs, decision making, quality of life and daily living, supportive care, and end-of-life care. In addition, 6 cancer centers from around the world are profiled to understand the approaches to patient care.



SECTION 2: **POLICY, SOCIETY, AND COMMUNITY IMPACT**

Assesses health policy, economic burden, public understanding of mBC, the impact of patient support and advocacy organizations, workplace perspectives, and the impact of mBC on caregivers and social relationships.



SECTION 3: **SCIENTIFIC LANDSCAPE**

Details the global burden of BC, history of progress in BC, the mBC innovation plateau, and the focus for the future.

STEERING COMMITTEE MEMBERS

This report would not have been possible without the guidance, direction, review, and support of the steering committee.*



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METHODOLOGY

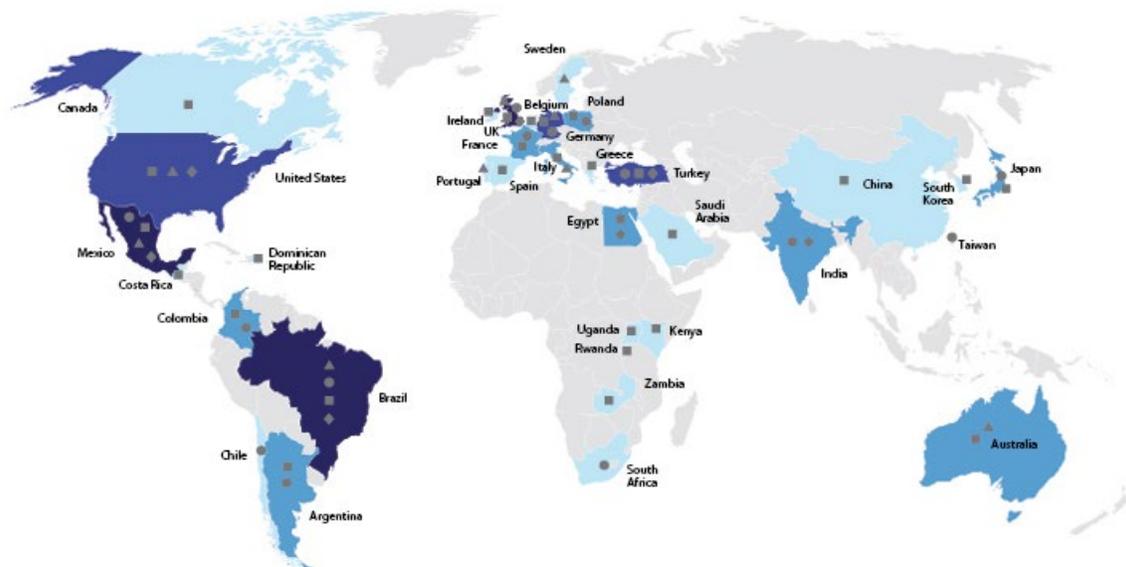
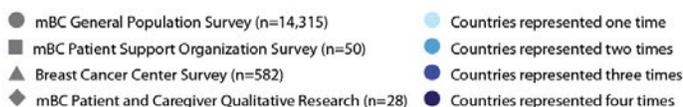
A multi-faceted approach was taken to assess the status of mBC and understand the many elements that impact patients living with metastatic disease. The report includes 4 global qualitative and quantitative primary research surveys conducted in 2015 and 2016 examining current perceptions of the state of BC in 34 countries around the world, including the first survey to analyze global public perceptions of mBC in multiple countries around the world. The new research surveys were conducted with:

- More than 14,000 adults among the general public in 14 countries

- Key members (CEOs, presidents and directors) of 50 patient support organizations focused on mBC, BC or general oncology in 28 countries
- 582 breast cancer center oncologists, nurses, and leaders (C-level administrators, medical directors of oncology) in 9 countries
- 28 patients with mBC and caregivers of patients with mBC in 7 countries*

Editor's note: Please see the [full report](http://www.BreastCancerVision.com) available at www.BreastCancerVision.com for detailed analyses and findings, methodology, appendices, terminology and considerations, full citations, and cancer center profiles.

Figure D
2015 and 2016 mBC Primary Quantitative and Qualitative Research



The report also discusses existing research with new analyses of BC resources and more than 3,000 previously published articles and abstracts. The analyses examined several key areas of mBC patient care and this report was the first of its kind to include a comprehensive analysis of the mBC scientific landscape.

In addition, in-depth interviews were conducted with 6 BC centers in different parts of the world to understand their unique approaches to patient care, as tailored to local patient needs and socioeconomic context.

*Other large studies of patient experience have been conducted, including the BRIDGE survey; MBC Alliance Landscape Analysis; Count Us, Know Us, Join Us; and Here & Now. Those findings also should be considered when evaluating patient experience.

SECTION 1 OVERVIEW: PATIENT CARE PERSPECTIVES

While there have been efforts to advance the management of mBC, considerable room for improvement in patient care remains. Patient care and support needs evolve along the care continuum and include: information and communication needs, decision-making, quality of life (QoL) and daily living, supportive care, and end-of-life care. Improvements in all of these areas can allow patients to lead more fulfilling lives.

Key Findings and Ongoing Needs

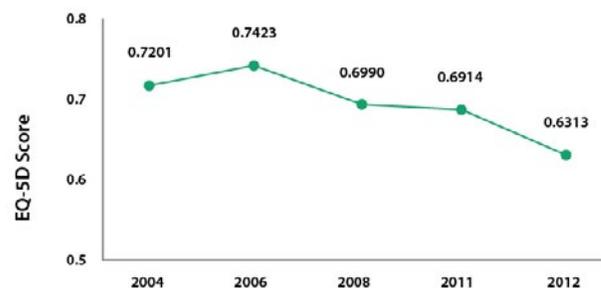
A higher quantity, quality, and specificity of mBC information is needed. mBC patients have a hard time finding the information they want and need. A report exploring the individual experiences of patients with mBC found that the information and support provided to them is inadequate compared to the services available at the time of an initial diagnosis of eBC. (Johnston, 2010) Contributing to this issue, healthcare providers often lack materials and resources for patients (Breast Cancer Center Survey, Pfizer, 2015), and information/support offered through patient support organizations (PSOs) is more frequently targeted to those with early disease. (Patient Support Organization Survey, Pfizer, 2015)

Patients want holistic, individualized, compassionate, and culturally sensitive dialogue with their healthcare professionals, which can support shared decision making. Communication between patients and physicians needs to better reflect each patient's unique attitudes about and experiences with mBC. The challenge in reaching this goal is evidenced in part by the fact that 44% of patients do not tell their healthcare providers about their goals for therapy. (Breast Cancer Center Survey, Pfizer, 2015) Honest communication is particularly important given common patient misperceptions about mortality, pain, treatments, and the possibility of being cured, (Breast Cancer Center Survey, 2015) and that physicians tend to minimize the severity of metastatic disease to patients. (A Story Half Told, Pfizer, 2014) This is reflected in the fact that **only 43% of healthcare professionals surveyed globally were trained to have difficult conversations with patients.** (Breast Cancer Center Survey, Pfizer, 2015)

A sound relationship between patients and their physicians and ensuring that choices align with a patient's desired degree of participation are essential tools for making complex joint decisions regarding treatment and patient care. This is particularly true when balancing goals of therapy, drug toxicities, QoL, and uncertain outcomes. (Filleron, 2015; Grunfeld, 2006)

QoL for those with mBC has not improved in the last decade. The ability to enjoy life as freely as possible from the physical, emotional, and financial burdens of mBC is crucial for patients. Unfortunately, an analysis of trends conducted for the report indicated that **QoL has not improved for patients with mBC in the last decade, and in fact, may have decreased slightly.**

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 in the full report



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.

This lack of improvement in QoL may be underscored by a failure to address remaining unmet needs. More research is required to determine what approaches, such

as referral services, create the greatest benefit in resolving QoL concerns. (Mosher, 2013) While there are numerous treatments available for mBC and more in development, they may not be able to address factors that may impact a patient's QoL, such as physical side effects and emotional well-being. (Please see appendix 1.3 in the full report for detailed methodology.)

Further complicating the ability to gauge QoL is that no standard definition exists for the term in clinical practice at the individual patient level, (Danesh, 2014) and the standardized and validated instruments for measuring QoL in clinical trials are not used in clinical practice. (FACIT.org; EORTC.org; Osoba, 2011) This makes it nearly impossible to determine if an individual patient's needs are being addressed or met.

mBC has far-reaching effects on QoL, which patients view as a major area in need of improvement.

The physical, psychological, and financial burdens of mBC greatly affect a patient's overall well-being. Yet, patients feel that their QoL issues are discussed quickly and vaguely. (Danesh, 2014) Patients report that fatigue, insomnia, lack of concentration, neuropathy, and pain have the greatest effect. (mBC in Canada, 2013; Danesh, 2014) In addition to distress, depression, and anxiety, they also experience social isolation, feelings of reduced self-worth, and sexual dysfunction. (Luoma, 2004; Banning, 2014; Milbury, 2013) Eight out of 10 patients feel that QoL is the biggest area in need of improvement in mBC care. (Here & Now, Novartis, 2013)

In addition to QoL issues, emotional support and treatment adherence are other key areas in which patients are in most need of additional support.

Emotional support and QoL improvements are the top 2 patient needs as identified by BC centers. (Breast Cancer Center Survey, Pfizer, 2015) Among breast cancer centers surveyed for this report, 78% of them offer emotional/psychological services to BC patients, but only 5% provide specific services for mBC. (Breast Cancer Center Survey, Pfizer, 2015) Despite the impact of mBC on psychosocial health, only 1/3 of patients with significant anxiety or depression access mental health services. (Mosher, 2012) If not addressed early, manageable emotional burdens can quickly escalate (Mosher, 2012), thus making it an important area for clinicians to address with patients.

Patients also need help adhering to treatment regimens. In the US, approximately 1/3 of patients with mBC engage in nonadherent treatment behavior, such as forgetting

A DECADE OF PROGRESS IN PATIENT CARE

- Some educational materials geared specifically toward mBC, such as guides to currently available resources and questions for patients/caregivers to ask their physician, do exist, and many physicians view them as helpful. (Breast Cancer Center Survey, Pfizer, 2015)
- Some countries offer guidelines and information on advanced care planning to support joint patient-physician decision making.
- QoL is being measured and included in many quantitative and qualitative patient care perspective surveys; standardized and validated instruments exist to measure QoL in clinical trials.
- Evidence-based guidelines from around the world, including high- and low-income countries, recommend supportive and palliative care in mBC. (Cleary, 2013) Palliative care is now advocated as a global human right. (Gwyther, 2009)
- New approaches to delivering supportive care, such as specialized nurses and teams for specific care services, have been successfully implemented in certain areas.
- Guidance on palliative care is more widely represented in the literature. (Cleary, 2013; Cardoso, 2013)

to take medication or not taking it due to side effects. (daCosta DiBonaventura, 2014) Poor compliance is a major problem in lower income parts of the world due to lack of national funding and access to adequate healthcare. (Adde, 2013; Abuidris, 2013; Adesunkanmi, 2006) Patients may have to bear the burden of transportation costs as well as the cost of diagnosis, overall care, medications, food, and accommodation during treatment. (Adde, 2013; Abuidris, 2013; Adesunkanmi, 2006)

Support for healthcare professionals is often overlooked. Healthcare professionals treating patients with mBC have reported a significant negative psychological impact on themselves. In a US survey, 42% of oncologists said that treating patients with mBC had a significant negative emotional impact on them, which may be due to limited treatment options. (Count Us, Know Us, Join Us,

Novartis, 2014) Even experienced healthcare professionals may experience a degree of psychological stress when delivering difficult information, including discussions about death, to their mBC patients. This highlights the importance of adequate training and psychological support for healthcare professionals.

More support and palliative care training, especially regarding pain management, is needed for healthcare professionals. Nurses report a lack of training, confidence, and tools to provide adequate palliative care (ie, care to improve QoL when active treatment is no longer given). (Cleary, 2013) Further, more than 40% of breast cancer centers surveyed for this report do not offer palliative care services specific to mBC patients. (Breast Cancer Center Survey, Pfizer, 2015) In addition, although palliative care is now advocated as a human right (Gwyther, 2009), patients in some developing countries do not have access to effective pain medications, including morphine.

A significant effort is needed to ensure that patients' and families' wishes at the end of life are met. Conversations about end-of-life are extremely difficult, yet it is crucial for healthcare providers to clarify patient and family preferences about care, location, and other requests. (Irvin, 2011) In fact, **65% of end-of-life discussions are held too late, after multiple changes of treatment** (Breast Cancer Center Survey, Pfizer, 2015), and many patients do not get a timely referral to hospice, missing out on the full benefits of this care. (Irvin, 2011;

Casarett, 2007) Additionally, many existing models of care in mBC are centered on institutional care (Cleary, 2013), yet the majority of patients around the world prefer to be in their homes at the end of life. (Gomes, 2013)



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

EMERGING RECOMMENDATIONS

Truly driving change in patient care requires the attention and action of a multi-stakeholder group. Key actions identified in the *Global Status of mBC Decade Report* include:

For healthcare professionals:

- Participate in mBC-specific training on how to better communicate with patients regarding their disease.
- Engage in sensitive and realistic discussions about treatment goals and end-of-life matters earlier in the mBC treatment pathway.
- Place greater research focus into the factors that impact QoL and effective psychosocial interventions to maximize QoL in mBC patients.

For healthcare professionals, patients, and caregivers:

- Engage in conversations and shared decision making regarding care and treatment, including QoL issues and end-of-life matters.

For healthcare professionals and PSOs:

- Empower mBC patients and their caregivers through information sharing and knowledge expansion regarding their disease and treatment options.
- Work together to provide a multidisciplinary, holistic, and individualized approach to mBC patient care.

Additional emerging recommendations can be found in the full report, available at www.BreastCancerVision.com.

SECTION 2 OVERVIEW: POLICY, SOCIETY, AND COMMUNITY IMPACT

Consideration of the societal factors that directly and indirectly shape the patient experience is vital to a holistic understanding of the disease. This includes policy perspectives, economic burden, societal experience/public understanding, media depiction of the disease, the impact of patient support and advocacy organizations, workplace perspectives, and the effect of mBC on caregivers and social relationships. Much work needs to be done to facilitate an overall environment that supports mBC patients.

Key Findings and Ongoing Needs

Many countries have not yet adopted national cancer plans (NCPs), and there are numerous challenges to country-level implementation of BC policies. According to the World Health Organization, 40% of countries do not have an NCP (a public health program designed to reduce cancer incidence, morbidity and mortality), and almost 75% of countries in Africa do not have a well-defined cancer plan. (WHO, 2013) Existing plans tend to focus on early detection and screening, which do not address the needs of patients with metastatic disease. (OECD, 2013a.) An analysis conducted for the *Global Status of mBC Decade Report* showed that **across the 29 cancer plans reviewed in detail, the United Kingdom referred to mBC specifically.** Part of the problem is the lack of reliable global prevalence statistics for mBC. Despite clinical and technological advancements such as electronic health records (EHRs), disease registries, and surveillance systems, even policymakers in high-income countries still lack reliable data regarding the burden of mBC. (Frederix, Breast Cancer Research and Treatment, 2013; Bonastre, 2012; Thomas, 2009) Without access to accurate numbers, policymakers cannot make informed policy decisions and prioritize resources where they are needed.

mBC is associated with a significant and rising economic burden to society and healthcare systems around the world as well as to individual patients and their families. While direct per-patient costs (hospitalizations, medical care, medications, etc.) vary by country, several studies show total costs over the course of mBC, including relapsed BC, range from €36,000 to €48,000 in Belgium, the Netherlands, France, and the UK. (Frederix, Breast Cancer Research and Treatment, 2013; Bonastre, 2012; Thomas, 2009) An analysis of patients in the US covered by the government health plan, Medicare, showed

that costs per patient were \$153,421 from diagnosis to death (median period of 26 months) (Davis, 2010); another study estimated costs at \$250,000 on average for privately insured patients. (Montero, 2012)

The economic burden of mBC goes far beyond direct costs of care. When indirect costs are added – such as those associated with lost wages for time off of work for patients and caregivers, unpaid caregiver time, and productivity losses for society – the financial toll is substantially greater. A US study estimated that the national economic burden of mBC due to lost productivity was nearly \$3 billion over a 5-year period, with total direct and indirect costs to society totaling more than \$12 billion – a three-fold increase from the 1990's. (Sorensen, 2012)

In a primary research study across 9 countries, 31% of respondents identified financial support as a top 5 unmet need for patients. (Breast Cancer Center Survey, Pfizer, 2015) **For patients under the age of 65, the indirect costs of mBC stemming from lost patient and caregiver wages 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) US data show that families with mBC incurred nearly 40% higher indirect costs compared with those families of patients with eBC. (Wan, 2013) Reductions in income can be significant, with 1 in 10 patients with mBC describing a 50% fall in household earnings in 1 study across 11 European countries. (Here & Now, Novartis, 2013)

This reduction in income comes at a time when expenses are likely to be increasing, and in some countries, as health insurance companies shift more costs such as higher payments for medications to patients. (Irwin, 2014) It is critical

A DECADE OF PROGRESS IN POLICY AND ADVOCACY

- Government, professional societies, and PSOs have played a critical role in developing health policy that is leading to better care for mBC. For example:
 - In 2015, the European Parliament, backed by Europa Donna, adopted a declaration that women with mBC have access to and be treated in specialist BC units.
 - Professional groups including the American Society of Clinical Oncology, St. Gallen breast cancer scientific committee, The National Comprehensive Cancer Network® (NCCN®), and the International Consensus Conference for Advanced Breast Cancer (ABC) have published guidelines calling for specific and tailored care for patients with mBC.
 - European School of Oncology Breast Centers Network and the Europe against Cancer European Breast Cancer Network aim to strengthen the evidence base for cancer care, supporting policymakers to develop national plans for BC.
 - PSOs such as Breast Cancer Network Australia (BCNA), Europa Donna, and Susan G. Komen have contributed significantly in capturing the experiences of mBC patients and bringing them to the attention of policymakers.
- In the US, the National Breast Cancer Coalition launched Breast Cancer Deadline 2020, a call-to-action for policymakers, researchers, BC advocates, and others to know how to end deaths from the disease by 2020.
- In Europe, Europa Donna is advocating for the European Parliament Written Declaration of Breast Cancer as well as other projects to raise awareness of the needs of mBC patients in policy and BC guidelines.
- In a major step forward for mBC patients around the world, the essential medicines list for the 2013 World Health Organization Global Action Plan for non-communicable diseases includes chemotherapy, hormonal therapy, and HER2-targeted medicines. (WHO, 2015)
- In 2012, a recommendation to collect data on patients with recurrent and metastatic BC cancer was made in the UK. (NCIN 2012)
- As a result of efforts by the Metastatic Breast Cancer Network, an advocacy group in the US, October 13 has been recognized as National mBC Awareness Day since 2010, drawing attention to the disease mainly in the US and Europe. (Metastatic Breast Cancer Network, 2010)
- Public exposure to mBC messages in the media has been increasing steadily since 2006, fueled by awareness initiatives, high profile patient stories, and advances in treatment.

for governments to consider the total direct and indirect costs of treatment as well as the impact of mBC on patients, families, and society for more informed policy decisions.

Misperceptions and lack of awareness about mBC are widespread around the world. A 2014 US survey found that 61% of the general population knew little to nothing about mBC. (A Story Half Told, Pfizer, 2014) In another study conducted in 14 countries, **74-87% of survey respondents incorrectly believed that early detection and/or treatment will prevent disease progression, and 48-76% incorrectly believed that advanced BC is curable.** While in developed countries 70-80% of patients diagnosed with eBC will not progress to advanced disease, the number is lower for those in less developed countries where treatment standards for eBC may be less advanced and patients are more often diagnosed at an advanced stage of the disease. (O'Shaughnessy, 2005; EBCTGG, 2015) Further, some see mBC as a disease not worth treating compared with eBC. (mBC General Population Survey, Pfizer, 2015) These findings are not

surprising given this report identified a lack of specific, robust public information about mBC from trustworthy sources and that less than half of the global general population feels that reliable information on advanced or metastatic BC is easy to access. (mBC General Population Survey, Pfizer, 2015) In the landmark global BRIDGE survey of mBC patients, 73% of respondents wanted increased public awareness of mBC, including more media attention for people living with the disease (60%). (BRIDGE Metastatic Breast Cancer Patient Survey, 2010)

Public misunderstanding of mBC and the resulting stigmatization and isolation patients feel have profound consequences for patients. In a new Pfizer study, **18-49% of the general public felt people with advanced or metastatic BC should not talk about it with anyone other than their physician.** This attitude was most common in India (49%) and Turkey (42%). (mBC General Population Survey, Pfizer, 2015) This attitude is particularly harmful in less developed countries where local attitudes and beliefs can discourage

patients from seeking care early on and contribute to poor outcomes. (Shulman, 2010)

Half of patients with mBC report feeling isolation and shame, even within the BC community. (mBC Alliance, 2014) Stigmatization of mBC increases a patient's health risks, isolates them from relevant resources, and prevents them from accessing the medical and social support that are key to survival and maintaining QoL. It may also cause patients to delay going to a clinician until they are exhibiting symptoms of the disease. (LIVESTRONG report, Beckjord, 2012; Tfayli, 2010)

Despite the vast and unique needs of mBC patients, PSOs typically devote more programming, resources, and funding to eBC. PSOs that focus on mBC, BC, or cancer in general acknowledge that a lower proportion of their efforts are directed toward mBC, often because PSOs perceive mBC as a smaller patient population and their resources are funded accordingly. (Patient Support Organization Survey, Pfizer, 2015) However, this perception is challenged by the reality that in some parts of the world, such as developing countries, 50-80% of patients are initially diagnosed with advanced disease. (Unger-Saldana, 2014) In addition, while peer support is particularly important to mBC patients, PSOs admit that true peer support is difficult to achieve. This can be due to a desire not to build an identity based on having mBC, being less physically active, an overall reluctance by patients to participate, or patients may find it traumatizing if a peer progresses or passes away. (Patient Support Organization Survey, Pfizer, 2015)

In most regions of the world, PSO activity in policy and advocacy specific to mBC is limited. PSO involvement in policy and patient advocacy varies by region, but across the board these organizations reported less mBC-specific advocacy work than for general BC. Whereas 70-89% of PSOs engage in policy and advocacy for any stage of BC, only 50-59% do so for mBC patients. In developing countries, PSO efforts need to address basic issues such as access to radiotherapy and pain medications before specific mBC issues can be approached.

mBC patients returning to work face emotional, physical, and cognitive challenges. (Feuerstein, 2006; CBCN, 2010) For cancer survivors, returning to work can often mean a return to normal activities, social recovery and rehabilitation after cancer treatment, and improved well-being. (Islam, 2014; CBCN, 2010; Yoon-Jung, 2013) Many patients choose to return to work for financial and emotional reasons, (Story Half Told, Pfizer, 2014) but may find the situation difficult to maintain. One international survey found that half of all mBC respondents

who returned to work left within 1 year. (Corneliusen-James, 2011) In contrast to younger patients with eBC in the US who largely remained employed 1 year after diagnosis and reported a supportive working environment, (Rosenberg, 2015) patients from many regions around the world with mBC described their advanced disease as a barrier to return to work. (Islam, 2014; Tevaarwerk, 2010; Mehnert, Cancer, 2013) Indeed, BC progression, or a worsening of the disease, and treatment is associated with a lower probability of employment and reduced work productivity compared with those whose disease has not progressed. (Yin, SABCS, 2015)

Additionally, many employers and healthcare providers are not educated about the impact of mBC on work. (Nitkin, 2011; Yamauchi, 2013; Workplace Interview Transcript; Amir, 2010) Uncertainty about how long periods of wellness will last, disease progression and changing treatment plans, and invisible but lasting side effects of mBC treatment such as peripheral neuropathy and fatigue, have an impact on the patient and the workplace and should be considered by employers. (Workplace Interview Transcript) The return-to-work experience varies greatly and suggests limited formal employer governance about managing patients with cancer. Although cancer-specific policies may not be in place, in some instances patients may instead be covered by national or organizational policies and procedures designed to protect workers with long-term medical conditions. Despite this, some employees with cancer describe being well supported at work. (Cancer Council, Victoria, 2013; CBCN, 2010; Workplace Interview Transcript) New data specific to return-to-work experiences in mBC are now being generated. Research in the UK and Ireland is examining employment experiences of patients with BC. (Amir, 2011) Ongoing research in the US explores similarities and differences between workplace issues experienced by patients with mBC and eBC. (Workplace Interview Transcript)

Patients with mBC may actively reduce the size of social networks to those who matter most to them. Primary research conducted for this report showed that, in general, the quality of interpersonal relationships with caregivers and those close to patients are critical to patients' sense of well-being. However, patients either ignore the views of the wider community 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) This may be especially true in some low- and middle-income countries where some believe that mBC is contagious, perpetuating feelings of isolation and stigmatization for patients. (mBC

Patient and Caregiver Qualitative Research, Pfizer, 2016) As a result of these experiences, patients ignore or reduce contact with those they find less supportive or understanding. (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016)

Patients' spouses or children typically become caregivers. (Feiten, 2013) In some low- and middle-income countries, caregivers as well as doctors "protect" patients from their diagnosis (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016), reflecting a family-centered approach to decision-making. This is the opposite of a Western approach to informed consent and patient autonomy. (Aljubran, 2010; Chittem, 2015)

Ultimately, mBC patients rely on their caregivers and support networks for practical, emotional, and financial support. The presence of a caregiver is important for the patient's feeling of social support, as those who had a caregiver were more likely to report feeling satisfied with the social support that they received compared with patients who did not. (Mertz, 2013) However, in some cultures, mBC patients may try to protect members of their support network, especially close family, who may find the situation difficult to handle, which can create a feeling of distance in the relationship. (mBC Patient and Caregiver Qualitative Research, Pfizer, 2016)

Support for caregivers is often overlooked. In a US survey of mBC caregivers, 50% felt that no one understood what he or she was going through. (Mayer, 2015) Besides the typical worries over a loved one's well-being, caregivers can face economic, psychologic, and marital/family strains. (Grunfeld, 2004; Hasson-Ohayson, 2010; Hasson-Ohayson, 2014; CBCN, 2010) Stress can also result in the caregiver neglecting his or her own self-care needs (Blum, 2010), with some studies showing that the distress experienced by spouses/caregivers may be greater than that of the patient themselves. (Grunfeld, 2004; Hasson-Ohayson, 2010) Further, distress may be greater in younger spousal caregivers than older ones and for men vs. women. (Hasson-Ohayson, 2010; Hasson-Ohayson, 2014) Spousal distress may go unnoticed when spouses are seen as caregivers, not as individuals in need of care themselves. (Hasson-Ohayson, 2010) Further, in a survey of BC care centers around the world conducted for this report, only half offered caregiver services. (Breast Cancer Center Survey, Pfizer, 2015) This may contribute to why caregivers describe wanting access to support services or support groups, but report being unable to find them. (Mayer, 2015)

EMERGING RECOMMENDATIONS

While health policy is lacking and negative perceptions and misunderstandings of mBC continue to exist globally, there are opportunities to drive change through improved education and awareness. Recommendations focus on continuing to inform relevant stakeholders on the role of policy, society, and community impact of mBC, with a recognition that negative perceptions and misunderstanding around mBC vary depending on each country and its resources.

For policymakers:

- Broaden the approach to health policy development beyond screening and early detection of BC to include greater support for mBC-focused research.
- Enact rights that meet the needs of employees with mBC and determine the changes required to facilitate a return to work after a diagnosis of mBC.

For PSOs and industry:

- Make investments in educational campaigns and outreach strategies to advance widespread global awareness and inspire action around mBC focused on the need for patient supportive services and improved treatments, in the same way that has been done for eBC.

For PSOs and healthcare professionals:

- Increase global access and availability of support services specific to mBC.

For all BC stakeholders:

- Develop a globally impactful alliance for mBC advocacy, replicating some of the successes seen by organizations such as the US mBC Alliance on a global scale, which include policy efforts, patient and physician communications resources, and disease awareness initiatives.
- Encourage media (both traditional and social) to deliver tailored, evidence-based approaches to mBC communication and education.
- Ensure there is a greater recognition of the impact of mBC on caregivers.
- Ensure there is a greater recognition of the financial impact of mBC on patients and their families as a step toward broader action.
- Increase understanding and awareness of the costs of mBC from an individual perspective as well as from a health system or societal perspective to enable the creation of financial support services and encourage appropriate financial planning.

Additional emerging recommendations can be found in the full report, available at www.BreastCancerVision.com.

SECTION 3 OVERVIEW: SCIENTIFIC LANDSCAPE

BC 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, with an estimated 43% increase in BC deaths by 2030. (WHO, 2013) BC is a heterogeneous disease that cannot be approached or treated in a one-size-fits-all fashion. Most major innovations in BC date back more than a decade, and eBC has benefited the most from them (see figure 3.1). Although some scientific progress in mBC has been made over the past 10 years, the level has differed across the 3 main mBC subtypes (hormone receptor-positive [HR+], human epidermal growth factor receptor 2-positive [HER2+], and triple-negative breast cancer [TNBC]). Innovation in mBC also has not kept pace with that in other metastatic cancers. Research efforts must be accelerated to realize the promises of precision medicine and improved understanding of the genomic underpinnings of mBC to transform patient outcomes.

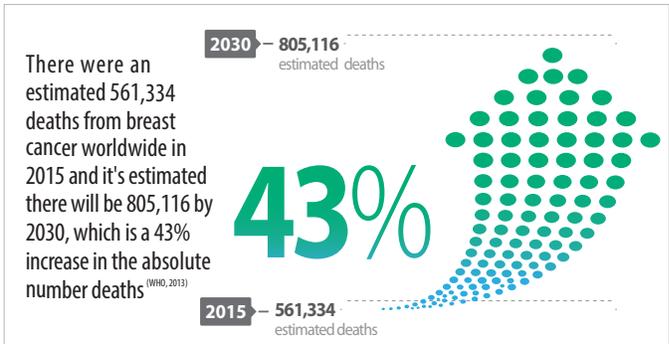
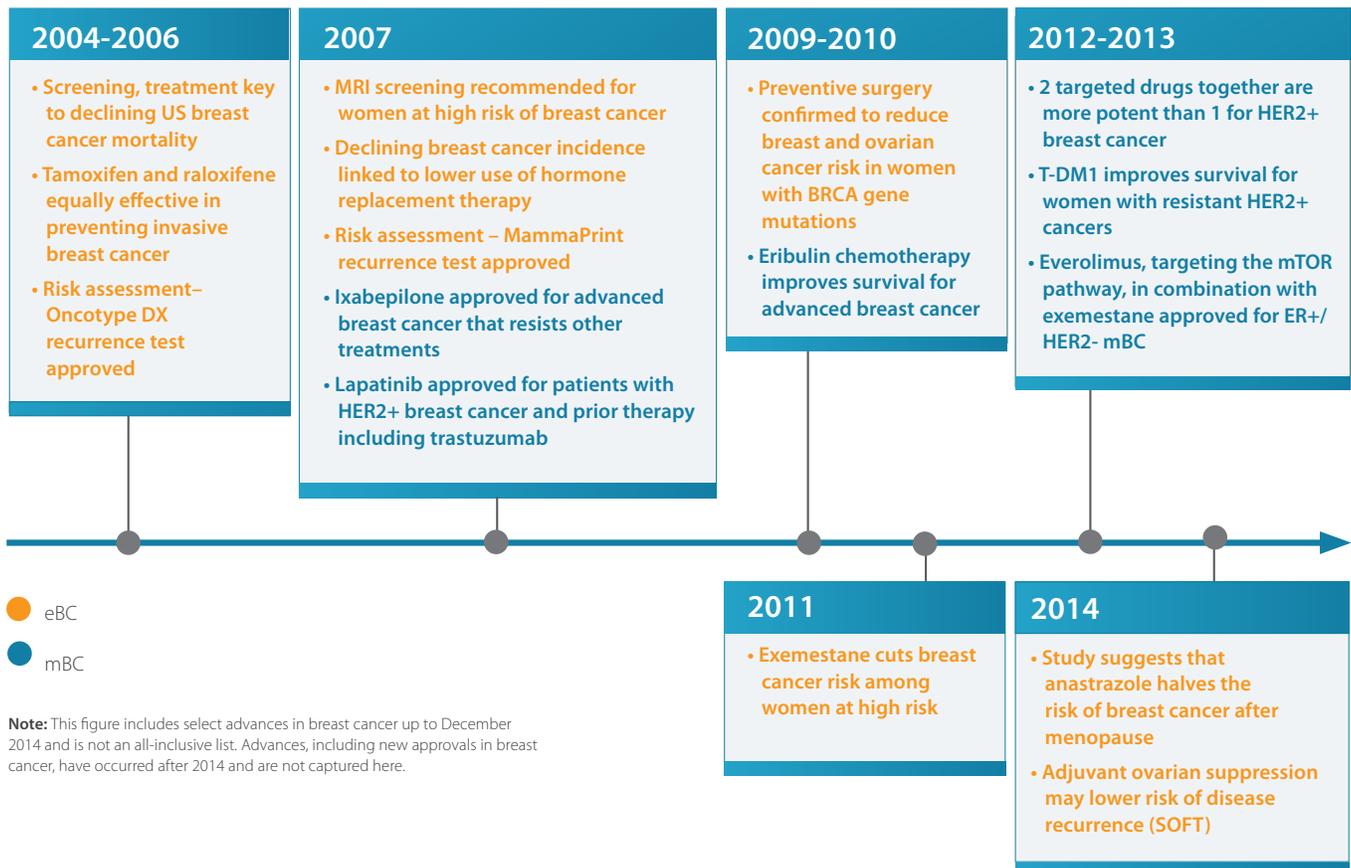


Figure: 3.1

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; NCI bevacizumab, 2015; Masters, 2015; Francis, 2015



Key Findings and Ongoing Needs

In the last decade, advances in mBC have been more incremental than in the past and have not been comparable across all mBC subtypes. Of the 8 therapies approved for BC in the last 10 years,* 5 are targeted agents and 3 are chemotherapy agents; **the majority were for HER2+ cancers**, which represent <15% of mBC cases. **Modest improvements in outcomes have occurred in HR+ cancer, and little to no improvements occurred in TNBC**, which together represent more than 80% of patients. (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; Howlader, 2014) The slowing pace of innovation in mBC is also demonstrated by a consistently low frequency of publications (about 7% of all BC research articles) and the need for more comprehensive and sophisticated treatment guidelines. (Cardoso, 2014; see figure 3.11 in full report)

Innovation in mBC also appears to be lagging behind that of other types of metastatic cancer, particularly in the last 5 years. Although new mBC therapies have been introduced, less scientific progress has been made in mBC than in other tumor types, including melanoma and lung cancer. Advances in the understanding of these 2 cancers have rapidly identified multiple clinically relevant subtypes, whereas mBC treatment is still guided by the 3 previously identified subtypes. Increased knowledge of melanoma and lung cancer also has been translated into precision medicine and immunotherapy, which are lacking in mBC. (ASCO BC, 2015; Bonotto, 2014; 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)

*Food and Drug Administration (FDA) approvals and clinical data in mBC are through 2014, and do not reflect new data and approvals in 2015 and 2016.

Figure: 3.2

Highlights of a Decade of Understanding of Disease in Select Tumor Types Through December 2014

ASCO BC, 2015; Bonotto, 2014; 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*	● 4	● 6	● 7
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.

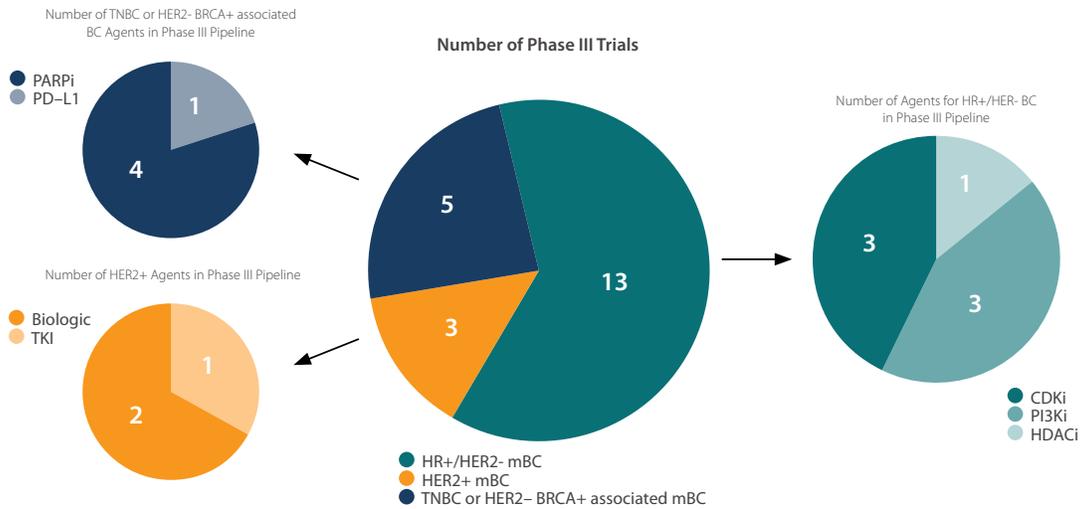
†Breakthrough therapy designation by the FDA started in 2013. Breakthrough therapy designation is granted when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, addressing an unmet need for a serious or life-threatening condition. Breakthrough therapy designation count includes all agents through September 15, 2015. (FCR, 2015; FDA breakthrough, 2015)

Progress in the Making

In recent years, there has been a substantial increase in research and development of new therapeutic approaches and targets. More than 20 Phase III studies with 15 investigational drugs for mBC are now open (clinicaltrials.gov). Phase III activity is greatest for HR+/HER2-mBC, with the cyclin-dependent kinase (CDK) inhibitor

class being the most advanced. Numerous trials exploring several different targets and strategies are also underway in TNBC. The fewest trials are in HER2+ mBC given the significant gains already made in this subtype; however, new approaches such as vaccines and antibody-drug conjugates are being explored.

Figure 3.3
Open, Interventional, Phase III Trials of Investigational Drugs in mBC by Subtype, ClinicalTrials.gov, September 15, 2015
 See Appendix 3.3 in the full report 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.

Overview of Scientific Progress in BC

Over a decade ago, there were significant BC innovations, including development of the first targeted therapies. These advances were built on a foundation of gains in understanding disease biology, risk stratification, and subtyping.

Most major innovations in BC have primarily benefited eBC, and they are credited with much of the decline in BC mortality, particularly in developed countries. (ASCO BC, 2015) In mBC, advances include the introduction of aromatase inhibitors for ER+ mBC in 1996 and HER2-targeted therapy in 1998. (Crighton, 1989; Bernard-Marty, 2004; Altundag, 2006; Genentech, 2015) Concurrent with these advances, median survival for mBC improved by 8 months during 1991–2001. (Albain, 2012) However, despite continued advances in mBC treatment during the past decade, there were only modest improvements in outcomes in mBC based on both real-world and clinical trial data. (Bonotto, 2014) Moreover, innovation has not been comparable across all mBC subtypes. Greater success has occurred in HER2+ mBC, with outcomes comparable to or exceeding those in HR+ mBC. (Dawood, 2010; FDA 2010, 2015; FDA 2012, 2015; FDA

2015, 2015; Bonotto, 2014; Swain, 2015; Verma, 2012; Yardley, 2013; Piccart, 2014; Doherty, 2015) Oncologists have been most frustrated by the lack of progress in increasing overall survival and the development of breakthrough treatments for TNBC. (TRM Oncology EPIC Report, 2015)

New innovations in mBC treatment are on the horizon. We have new types of patient-relevant endpoints in clinical trials that take into account extended time of disease control without loss of QoL and help clinicians, payers, and patients assess the clinical meaningfulness of therapy based on multiple parameters. Also, there are better registries and real-world data generation to gain greater understanding of the patient population as well as the true prevalence of mBC and recurrence from early to late disease. Further, new treatments 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)

EMERGING RECOMMENDATIONS

Achieving progress in mBC means turning mBC into a chronic disease with the potential to achieve lasting remission. Research efforts should be accelerated within industry and the scientific community to achieve this goal and could potentially focus on:

- Increasing the pace of innovation.
- Deepening our understanding of the underlying mechanisms of the BC disease process, including genomics, immune profiling, and further molecular subtyping, to inform the application of precision medicine.
- Increasing 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.

- Advancing treatment, including development of new targeted therapies and sequencing of therapies.
- Improving the way that we conduct clinical trials, collaborate on research, and demonstrate the value of new treatments.
- Developing more academic, professional, and patient alliances, which are crucial for optimal clinical development and patient management.

Additional emerging recommendations can be found in the full report, available at www.BreastCancerVision.com.

A VISION FOR THE FUTURE OF mBC

Today is our opportunity to change what BC will look like tomorrow because mBC patients deserve to live longer lives with improved quality of life, better care and treatments, greater understanding, and more effective advocacy. We encourage diverse stakeholders around the world to rally around patients with mBC and fulfill our shared vision for a more promising future, including the possibility that cures may be realized for certain patients.

This global call-to-action implores the entire breast cancer community and the global public to work alongside each other in developing solutions to address

the enduring challenges and unique unmet needs identified in this report. From this report and the detailed recommendations proposed, we hope to stimulate mBC discussions globally, inspire education, and drive change in patient care. Through these efforts, we strive to advance care and outcomes over the next 10 years.

mBC is a worldwide health concern that is complex and multifaceted. Together as a global community, we can work in solidarity to make a profound impact on the mBC landscape and to change the lives of countless people affected by this disease across the world.

The *Global Status of Advanced/Metastatic Breast Cancer 2005-2015 Decade 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.***

