GLOBAL STATUS OF mBC DECADE REPORT

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**
- **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**

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)

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	▼	▼

*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)

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'Shaugnessy, 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 ≤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)

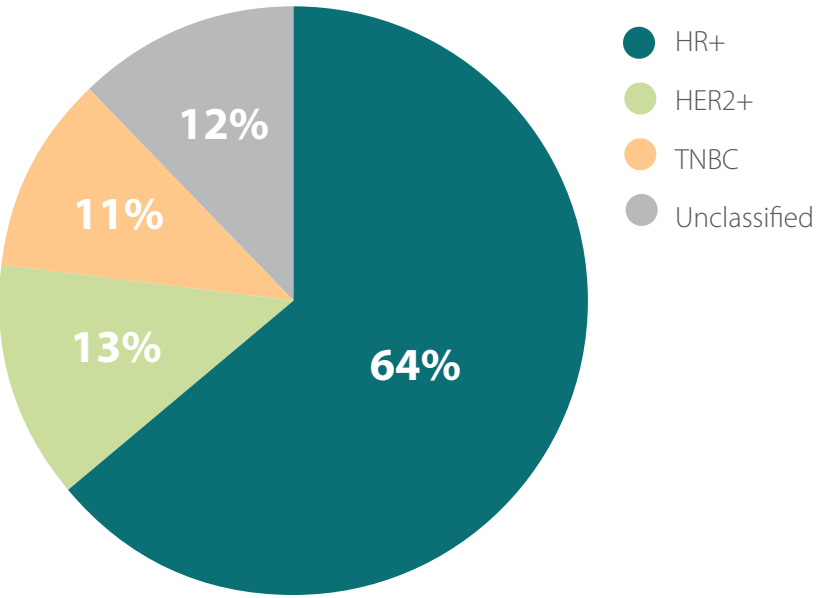
- **Triple-negative breast cancer (TNBC):** Heterogeneous group of tumors more recently categorized as a subtype of their own that does not express either PR, ER, or HER2. (Clarke, 2012; Allison, 2012; Lehmann, 2011) Although TNBC only represents <15% of total cases of breast cancer in developed regions 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.

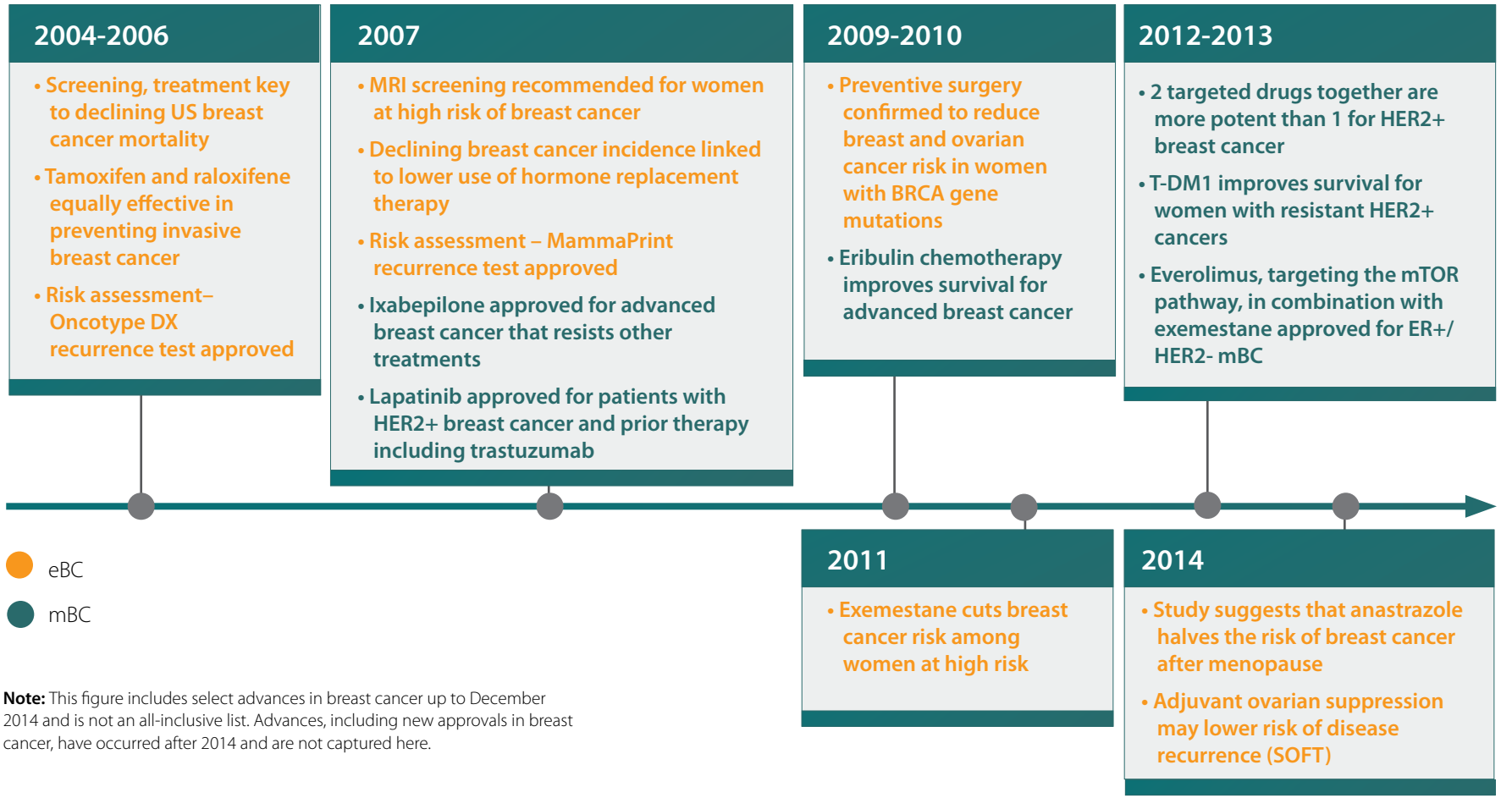
"Aspects of breast cancer treatment underlie much of the observed improvement in breast cancer mortality and survival between the 1970s and 2000s. Those decades saw remarkable scientific advances, including identification of the human epidermal growth factor receptor 2-neu (HER2-neu) oncogene and development of the targeted agent trastuzumab…"

Elkin EB and Hudis CA. J Clin Oncol. 2015;33(10):2837-2838.

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



Note: This figure includes select advances in breast cancer up to December 2014 and is not an all-inclusive list. Advances, including new approvals in breast cancer, have occurred after 2014 and are not captured here.

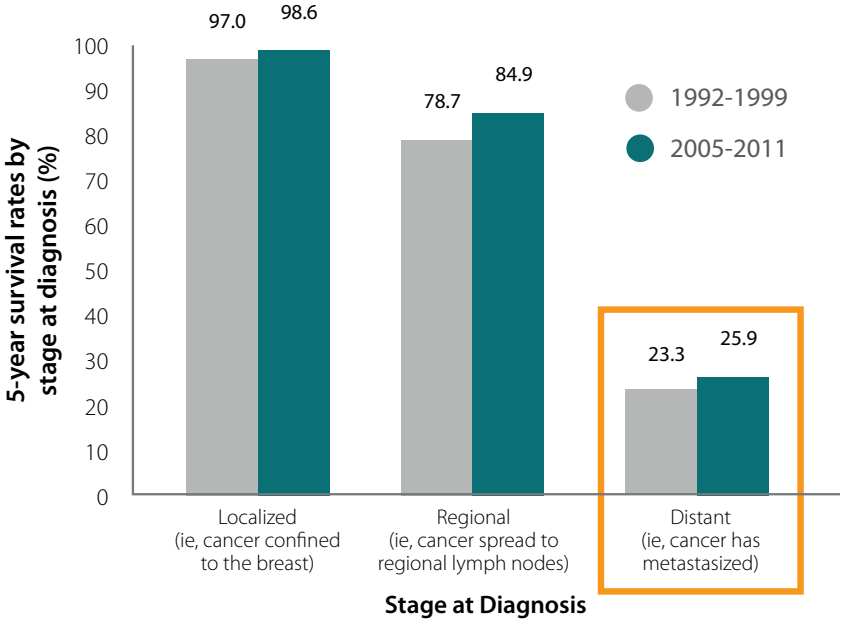
B There have been modest improvements in outcomes for patients with mBC in the past decade

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



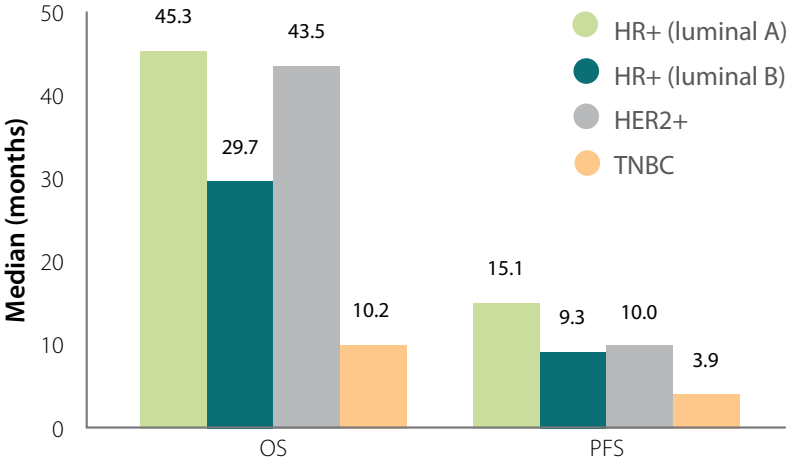
Scientific advances in the 1990s and 2000s are reflected in the improvement in outcomes in mBC during that time frame. (Albain, 2012) An 8-month improvement in median survival for mBC was observed from 1991 to 2001, corresponding with the introduction of AIs in the 90s for HR+ mBC, but subsequent progress 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

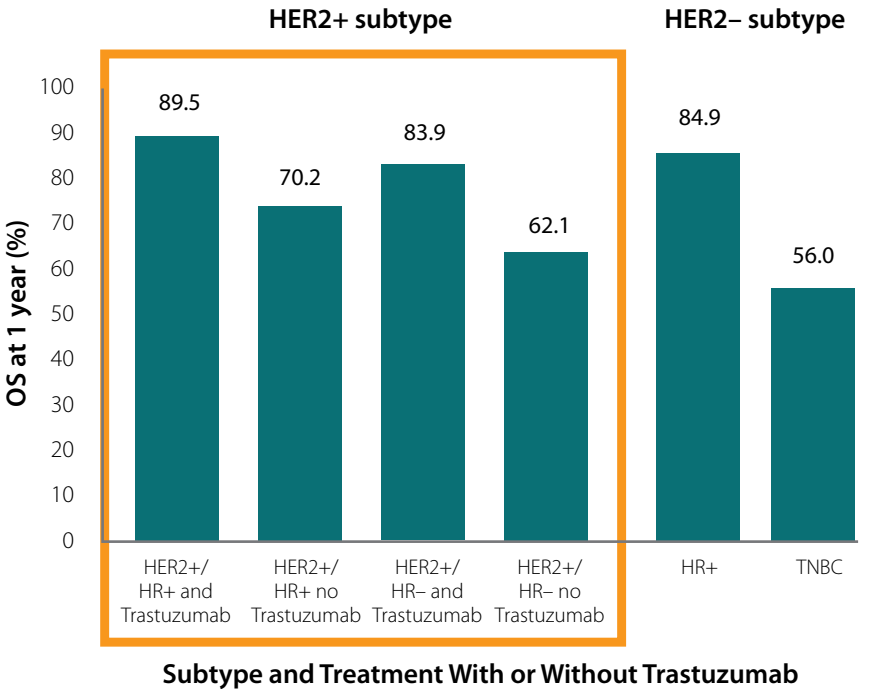


These data, while informative, highlight care provided within a specific period of time and may not fully capture the impact of more recent advances in the changing landscape of mBC treatment, particularly in the HER2+ space. The limited data available, from a study of women with mBC diagnosed between 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

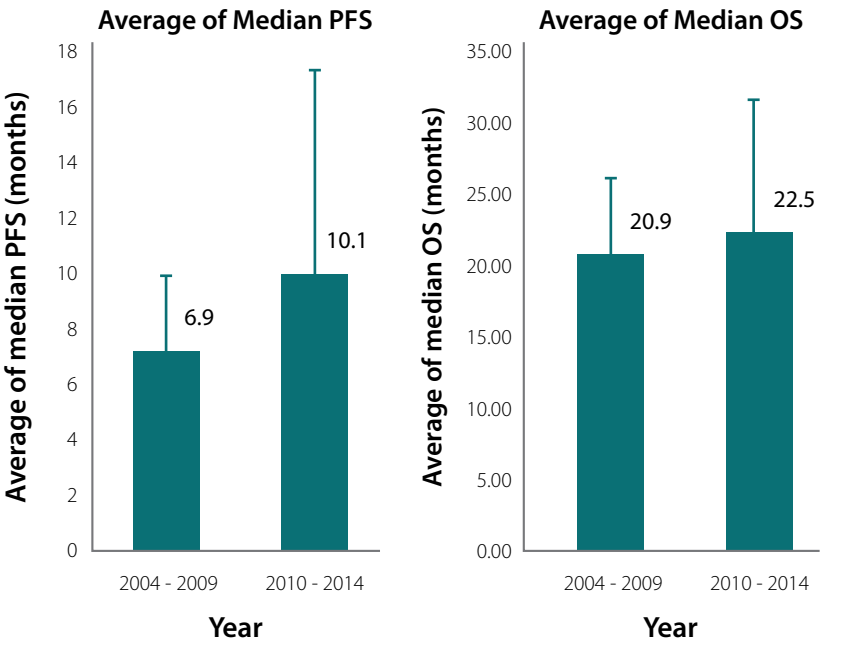
Dawood, 2010



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

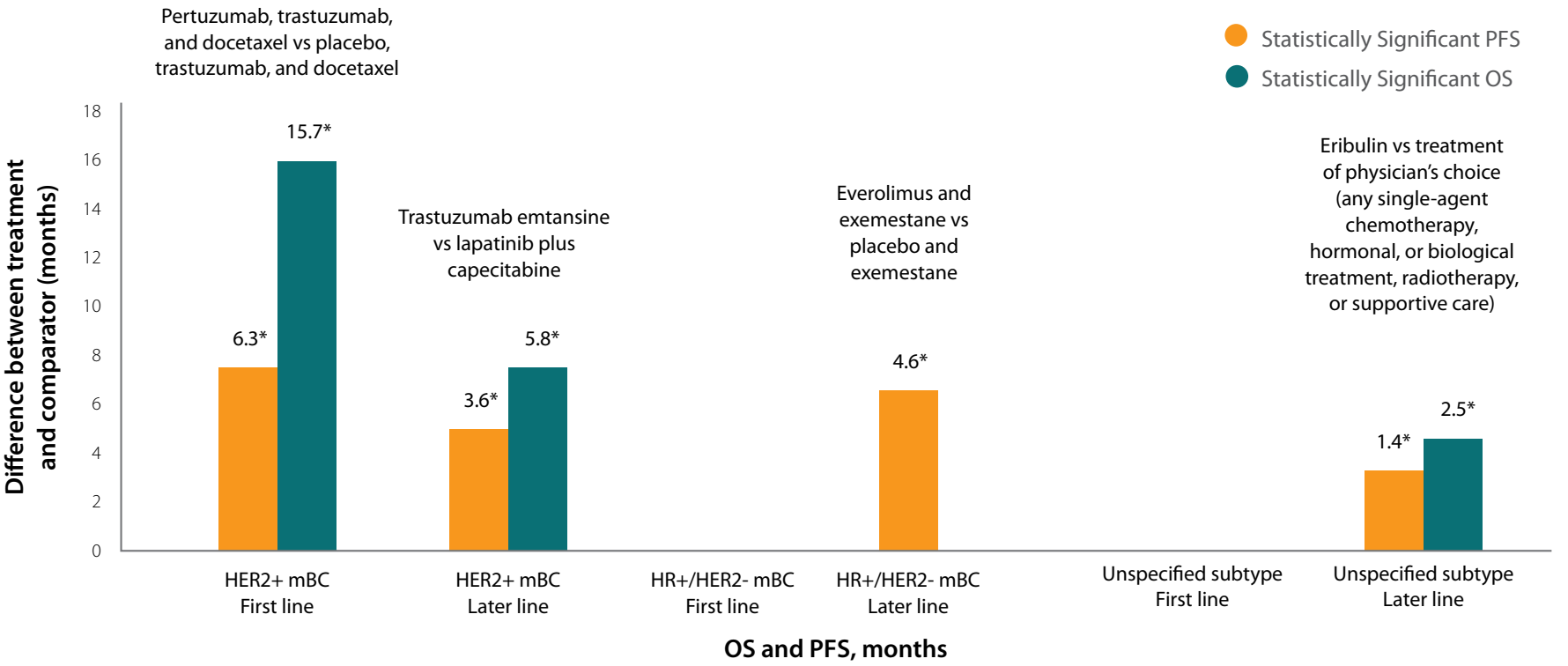


Diving deeper, improvements in mBC have not been equally demonstrated across all subtypes, particularly in TNBC, where oncologists have been most frustrated by lack of progress in increasing OS and developing breakthrough treatments. (TRM Oncology EPIC Report, 2015) Figure 3.8 below compares the changes (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

C 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 word 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; NCI eribulin, 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	enibulin 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)

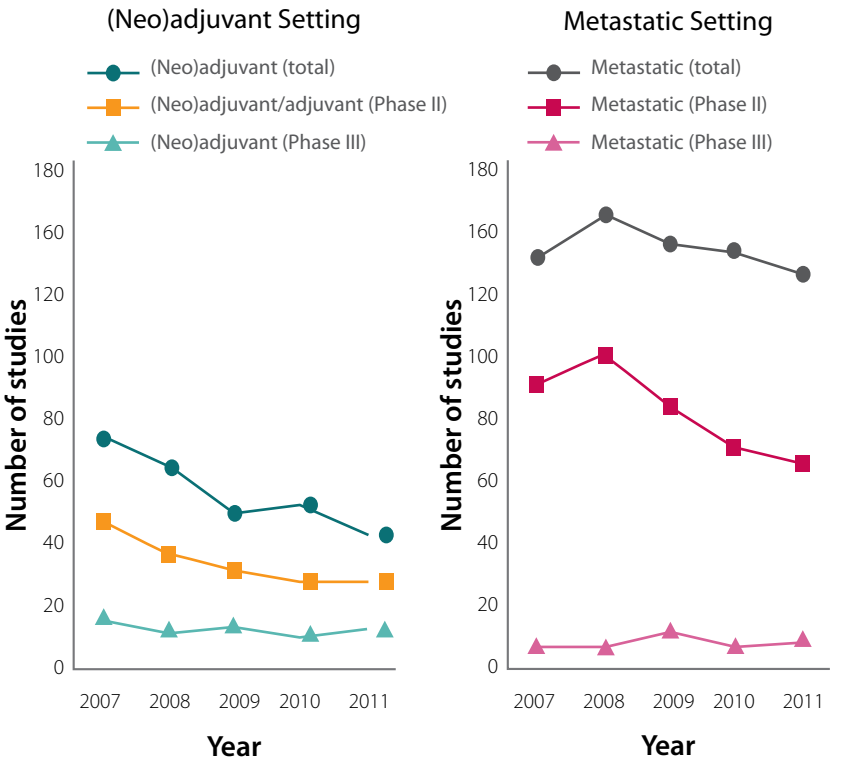
- Decreases in the number of patients enrolled (excluding outliers)
- Decreases in clinical trials focused on conventional and targeted therapies
- Decreases in small, Phase II trials in unselected populations
- Decreases in Phase II trials
- Increases in trials focused on symptom management

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

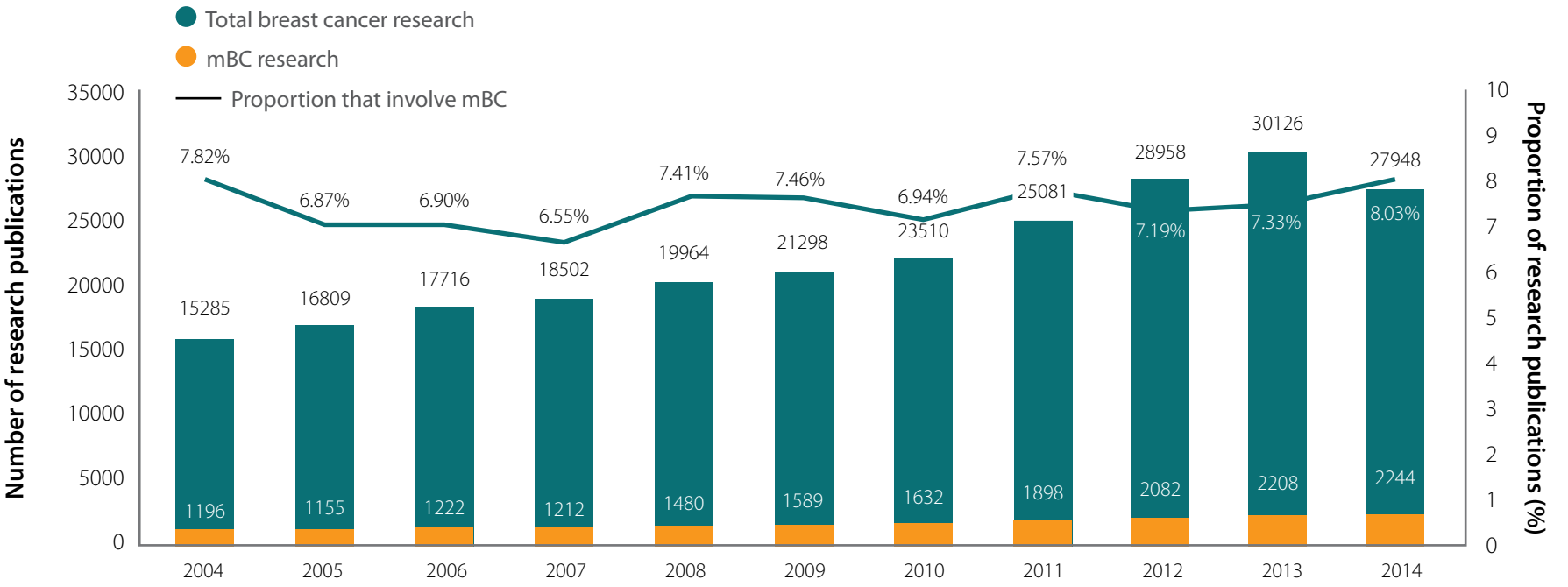


Note: Data are provided through 2011 and may not be generalizable to more recent years.

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

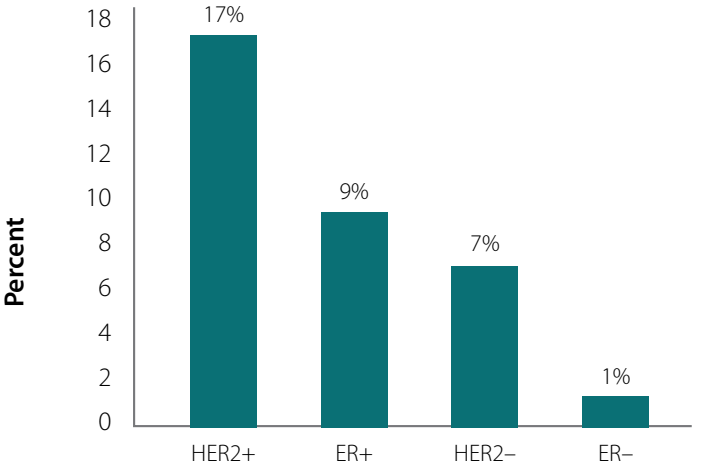


Database: SciFinder®. Key Words: "Advanced" OR "Stage IV" OR "Metastatic" + breast cancer. Year Range: 2004-2014.

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 3.13

Frequency of Subtypes in mBC Conference Abstracts

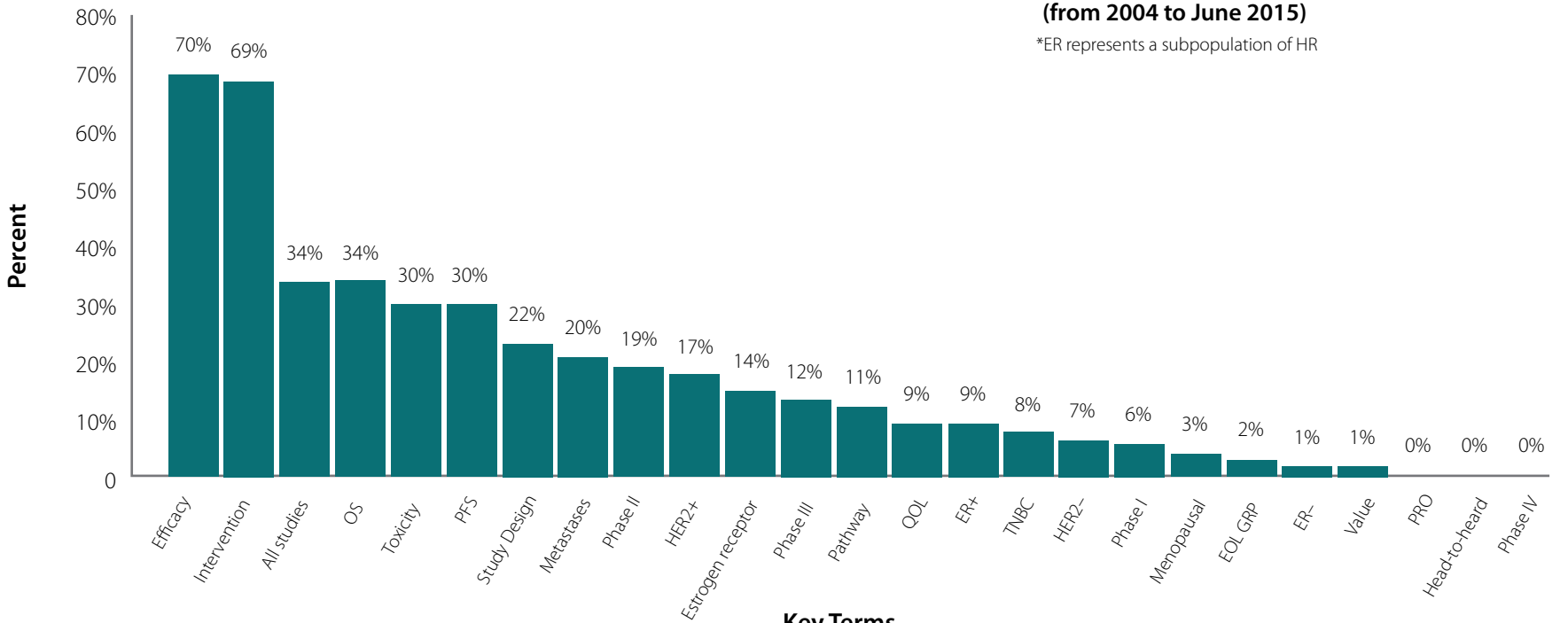


(from 2004 to June 2015)

*ER represents a subpopulation of HR

Figure 3.12

Frequency of Key Terms in mBC Conference Abstracts



Key Terms
(from 2004 - June 2015)

"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)
• Surgery	• General recommendations
• Radiation therapy	• Assessment guidelines
• Pathology	• General treatment guidelines
• Adjuvant therapy	• ER+/HER2- mBC
• Neoadjuvant therapy	• HER2+ mBC
• Use of bisphosphonates	• Chemotherapy and biological therapy
• Elderly vs young patients	• Specific sites of metastases
• High risk mutations	• Supportive and palliative care
• Breast cancer diagnosed during pregnancy	• Metastatic male breast cancer
• Pregnancy after breast cancer	
• Male breast cancer	
• Lifestyle factors	

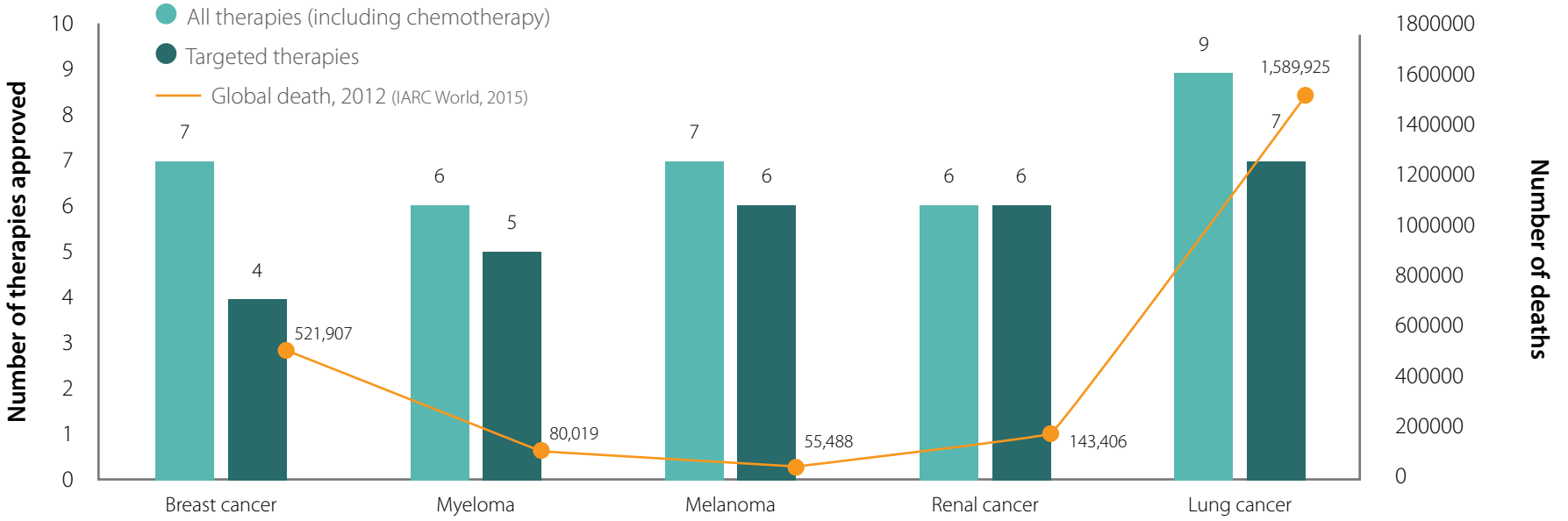
Note: Dates refer to the year the guidelines were published.

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. (FDA 2015, 2015; FDA 2012, 2015; FDA 2010, 2015; FDA 2006-2009, 2015; FDA ixabepilone, 2015; NCI paclitaxel, 2015; FDA 2011, 2015; NCI erlotinib, 2015; NCI sorafenib; 2015) In context globally, less than 55,000 deaths were reported due to melanoma in 2012 compared with an estimated 521,907 due to breast cancer, which highlights the significant disease burden and continuous need for innovation in the form of new drug approvals that have the potential of changing the natural course of 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 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)

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.)

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 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.

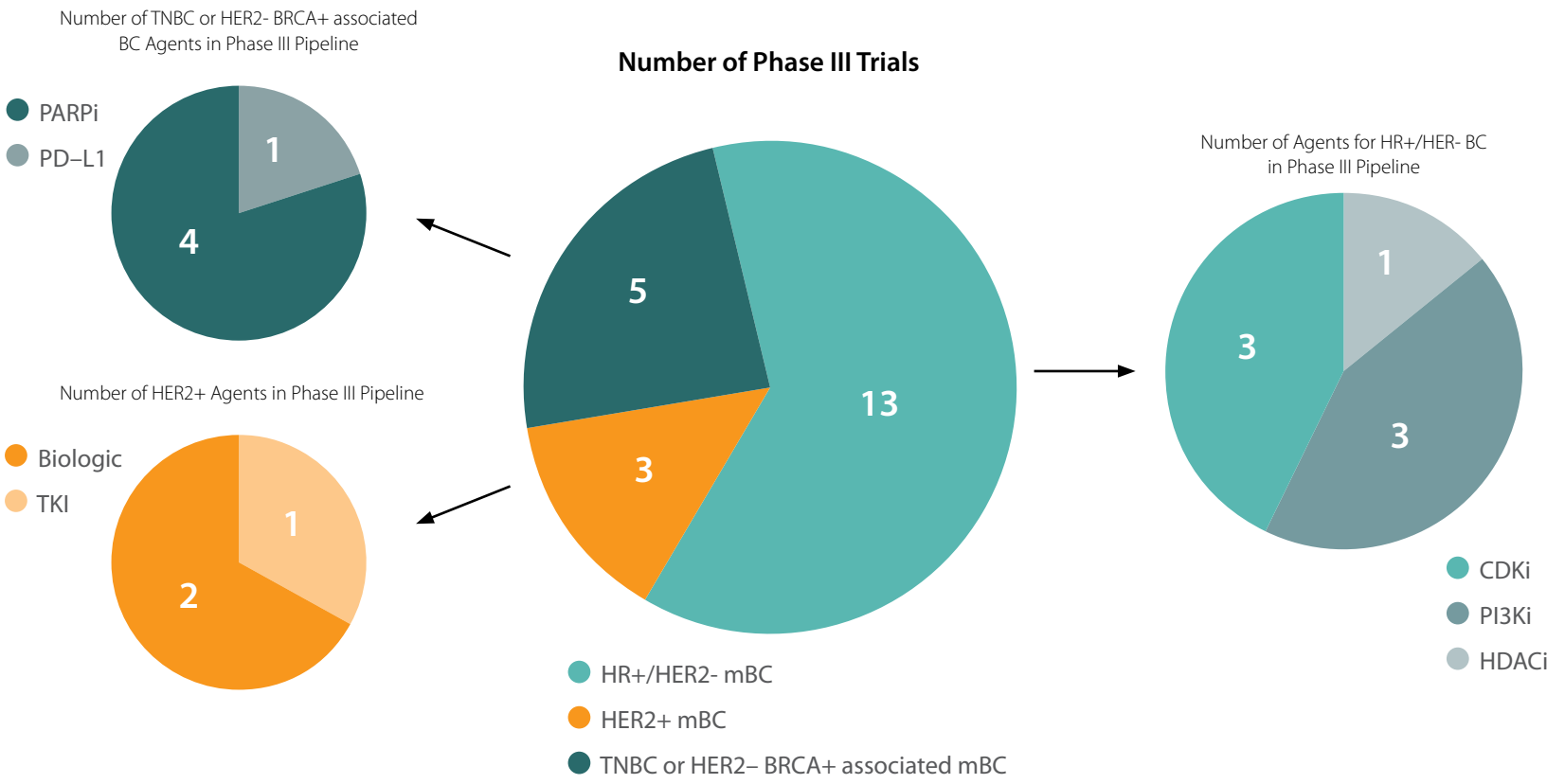
The high unmet need in TNBC is apparent, given the number of investigational drugs in Phase III studies, as well as large, randomized, Phase II studies of over 100 patients. The investigational drugs for TNBC include PARP inhibitors, antibody drug conjugates, and PD/PD-L1 immunotherapies. Many of the 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; CMTP, 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.

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

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.

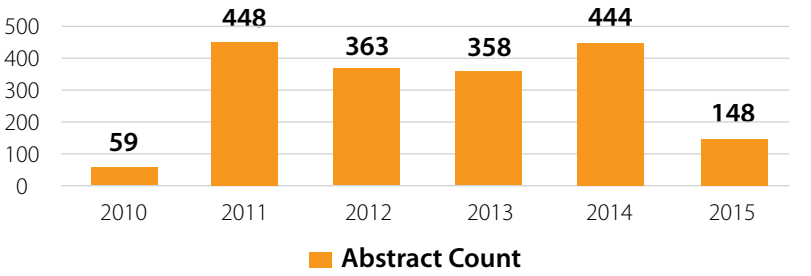
Method: A text-mining search was conducted with abstracts gathered from conferences covering mBC. This method searches for binary outputs of absence or presence by disregarding word order and grammar. To perform this analysis, all punctuation except for +, - and / was replaced with a space and content 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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