Metastatic Breast Cancer MBCalliance

MBCA's Top Priorities for People Living with Metastatic Breast Cancer (MBC)

1. ***Clinical Trials:*** **Accelerate clinical trial innovations.** Areas that will drive the most innovative clinical trial design include:
    - Broadening clinical trial eligibility
    - Inclusion of real-world data
    - Decentralization of trials
    - Inclusion of patient-reported outcomes (PROs)
    - Allowing patients to cross over to the treatment arm
    - Discussion about flexible dosing of a drug versus maximum tolerated dose

2. ***Diversity, Equity, and Inclusion:*** **Increase clinical trial enrollment of people living with MBC who have been historically excluded from treatment trials. Groups historically excluded from clinical trial include:**
    - Minority and underserved people
    - People with brain metastases

3. ***Leveraging Technology for Personalized Care:*** **Educate people living with MBC and healthcare providers (HCPs) about the most innovative and emerging testing options to inform personalized treatments.** Emerging testing options in MBC include:
    - Sampling body fluids for minimally invasive testing
    - Imaging tracers for minimally invasive testing
    - Testing for treatment response and recurrence in HER2+ breast cancer

4. ***Financial Toxicity:*** **Address financial toxicity in all aspects of living with MBC.** Efforts to address financial toxicity include:
    - Communication between HCPs and patients about anticipated expenses
    - Identification of sources of assistance and educational resources

5. ***Off-Label and Compassionate Use:*** **Provide timely, efficient access to expanded use (also called compassionate use) of investigational medications.** Efforts are needed to improve patient access to investigational medications:
    - Improvements to increase the efficiency for obtaining medications through compassionate use
    - Visibility and education on how to access such medications

6. ***Research Priorities:*** **Accelerate research in key areas.** Important areas of research include:
    - Delaying and overcoming treatment resistance
    - Understanding what causes metastasis
    - Investigating underrepresented areas of MBC such as triple-negative breast cancer (TNBC), lobular MBC, inflammatory MBC, brain metastasis, and leptomeningeal disease

7. ***Education and Communication:*** **Enhance education and communication between patients and HCPs.** Education and communication are needed in the areas of:
    - The importance of palliative care
    - The value of participation in clinical trials

RESEARCH	CLINICAL TRIALS	STANDARD OF CARE	QUALITY OF LIFE
			

1. *Clinical Trials:* Accelerate clinical trial innovations

Several areas of focus will drive the most innovative clinical trial design:

- Broadening clinical trial eligibility
- Inclusion of real-world data
- Decentralization of trials
- Inclusion of patient-reported outcomes (PROs)
- Allowing patients to cross over to the treatment arm
- Discussion about flexible dosing of a drug versus maximum tolerated dose

Clinical trial eligibility criteria are designed for patient safety and study integrity, but overly strict criteria can limit who is able to enroll in a trial, limit generalizability to a broader group of patients, and can lead to important differences between trial participants and real-world patients. Efforts are underway to broaden eligibility criteria by including patients with a lower performance status, various laboratory test results, brain metastases, leptomeningeal disease, organ dysfunction, other previous or current malignancies, and comorbidities, as well as by increasing the interval between tests[1-4]. Another way to increase generalizability is when clinical trials incorporate real-world data derived from electronic health records, previous clinical trials, registries, or claims data as an external control arm[5,6]. This type of control arm may more closely reflect everyday clinical oncology practice.

Multiple barriers exist that prevent sufficient enrollment of clinical trial participants. The need to travel to a trial site is a barrier that can be an impediment for people living in rural areas as well as those with childcare/eldercare responsibilities and those for whom travel is difficult. Decentralization of trials seeks to remove these barriers by implementing telehealth, local community-based medical centers, home-based delivery of investigational medications, and wearable devices[7].

PROs capture the experience of patients without interpretation by physicians or anyone else. HCP-reported outcomes are considered insufficient to capture the full patient experience. Understanding the patient perspective during treatment provides the best symptom management, quality of life, and disease-related outcomes, and may help with dose selection[8]. PROs are increasingly being incorporated into clinical trials, and standard practice is that all trials conducted by the Translational Breast Cancer Research Consortium (TBCRC)

are reviewed for incorporation of PROs. TBCRC provides recommendations for PRO measures that can be used in trials[9].

Allowing patients to cross over to the treatment arm after initial enrollment in the placebo arm addresses certain ethical concerns, but also limits the statistical analysis of data collected from a clinical trial, which can ultimately impact the drug's potential. Efforts are underway to address statistical analysis problems in trials in which crossover is part of the trial design[10].

Use of the maximum tolerated dose of a drug does not necessarily lead to better outcomes and may cause harm[11]. Discussions about flexible dosing options are a priority of the Patient-Centered Dosing Initiative[12].

Expanding eligibility requirements, decentralization, funding for inclusion of PROs, and testing different sequencing and dosing of drugs were identified as important areas of focus in the MBCA's Thought Leader project[13].

2. *Diversity, Equity, and Inclusion:* Increase clinical trial enrollment of people living with MBC who have been historically excluded from treatment trials

Groups historically excluded from clinical trial include:

- Minority and underserved people
- People with brain metastases

Enrollment of minority and underserved patients in clinical trials is lower than overall enrollment. Efforts aimed at specifically increasing enrollment of minority and underserved patients in clinical trials include increasing trust of HCPs by patients by deliberate support and compassion, use of culturally sensitive multilingual approaches that respect unique, proud cultural histories, attendance by HCPs at tumor boards to identify candidates for trial enrollment, hiring of trial coordinators of ethnically diverse backgrounds to communicate with patients, and incentivizing HCPs to enroll patients[14]. The BECOME project showed that Black women want to know about and would consider participating in trials, but they lack information, and that Black patients want to learn about trials from someone with the same racial/ethnic identity and health experience[15]. In addition to increasing enrollment of Black patients, people of color should have a voice at all steps of trial design and participation. Strategies to remove barriers to care and correct social determinants that lead to disparities in treatment outcomes in Black people living with MBC also need to be addressed[16].

Another group that has been historically excluded from clinical trials are people with MBC with brain metastases. Recent efforts to allow enrollment of these patients have led to an increase in enrollment[17]. The MBCA's Thought Leader project identified the importance of efforts to increase enrollment of Black patients and those with brain metastases[13].

3. *Leveraging Technology for Personalized Care:* Educate people living with MBC and healthcare providers (HCPs) about the most innovative and emerging testing options to inform personalized treatments

Testing options in MBC include:

- Sampling body fluids for minimally invasive testing
- Imaging tracers for minimally invasive testing
- Testing for treatment response and recurrence in HER2+ breast cancer

Recently, biomarkers beyond the estrogen receptor, progesterone receptor, and HER2 have emerged that can be used to guide treatment decisions. Genetic testing and biomarker testing are recommended as part of the standard of care[18]. Recommended biomarkers are outlined in the most recent guidelines[18]. Many biomarkers can be detected through non- or minimally invasive tests that include sampling various body fluids and imaging[19-21]. A number of imaging tracers for detection of the estrogen receptor, HER2, poly (ADP-ribose) polymerase (PARP), and PD-L1 are in various stages of development[22,23]. Innovative genomic biomarker tests, such as for treatment response and recurrence in HER2+ breast cancer, are emerging[24]. The MBCA's Thought Leader project identified liquid biopsies as an area with high potential to impact people living with MBC[13].

4. *Financial Toxicity:* Address financial toxicity in all aspects of living with MBC

Efforts to address financial toxicity include:

- Communication between HCPs and patients about anticipated expenses
- Identification of sources of assistance and educational resources

Financial toxicity, defined as economic consequences resulting from cancer treatment, is a complex source of distress in people living with MBC and can be considered equivalent to the toxic side effects of treatment. Financial toxicity results from accumulation of costs due to insurance (e.g., co-pays), out-of-pocket expenses such as over-the-counter items, childcare and eldercare expenses, transportation costs, and lost income due to inability or reduced ability to work[25]. The cost of all treatment-related medications, including what insurance does and does not cover, should be communicated to the patient by a member of the healthcare team. Cancer Support Community provides a checklist to assist with understanding insurance coverage and options[26]. Assistance for patients in identifying resources, including community support, is available[27]. The MBCA's Thought Leader project found that addressing financial toxicity was an important area of focus[13]. Several breast cancer advocacy groups are addressing financial toxicity[28-33].

5. *Off-Label and Compassionate Use:* Provide timely, efficient access to expanded use (also called compassionate use) of investigational medications

Efforts are needed to improve patient access to investigational medications:

- Improvements to increase the efficiency for obtaining medications through compassionate use
- Visibility and education on how to access such medications

Compassionate use or expanded use allows people with serious diseases to try medications that are not FDA approved for their condition. The FDA provides information on how to qualify for and apply for expanded access[34,35]. However, increased visibility and education is needed that leads to timely and efficient access to these medications for patients.

6. *Research Priorities:* Accelerate research in key areas

Important areas of research include:

- Delaying and overcoming treatment resistance
- Understanding what causes metastasis
- Investigating underrepresented areas of MBC such as triple-negative breast cancer (TNBC), lobular MBC, inflammatory MBC, brain metastasis, and leptomeningeal disease

Resistance to drugs may be due to new, acquired mutations, changes in cell signaling, epitope masking (i.e., hiding of the drug target by the cell), target truncation (i.e., loss of the region of the protein to which the targeted drug binds), and increased efflux of the drug from cancer cells[36-38]. Combination treatments with immunotherapy or targeted therapy, as well as careful dosing and scheduling of DNA-damaging chemotherapy agents, may be important in the context of reducing treatment resistance[37,39].

Prevention of metastasis, which includes prevention of initial metastasis in a person with early-stage disease and prevention of new metastases in a person with MBC, remains an important but unmet goal for improving patient outcomes. Tumor cells interact with the microenvironment. These interactions can affect immune cells and molecules, other components of the extracellular environment, tumor cell survival, and drug resistance. Steps in metastasis that could be targeted include movement of tumor cells from the primary site, arrest of tumor cells at a new site, tumor cell dormancy, establishment of tumor cells in a new location (called metastatic colonization), and the genes and molecules involved in these processes[40].

Areas of investigation for treatment of triple-negative MBC include the use of CDK4/6 inhibitors, PARP inhibitors, and immunotherapy[41,42]. Areas of investigation for treatment of lobular MBC include CDK4/6 inhibitors, HER2-

targeted therapies, immune checkpoint inhibitors, phosphatidylinositol 3-kinase (PI3K) pathways inhibitors, and others[43]. Areas of investigation for treatment of inflammatory MBC include mitogen-activated protein kinase inhibitors, tyrosine kinase inhibitors, and immune checkpoint inhibitors[44]. Areas of investigation for treatment of brain metastases and/or leptomeningeal disease include the use of tyrosine kinase inhibitors and therapies (both small molecules and monoclonal antibodies) targeting HER2, vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), PI3K/mammalian target of rapamycin (mTOR), and others[45,46].

Treatment resistance and understanding the process of metastasis were identified as important research topics in the MBCA's Thought Leader project, and the project reported that little progress has been made in TNBC, lobular MBC, inflammatory MBC, or brain metastasis[13].

7. *Education and Communication:* Enhance education and communication between patients and HCPs

Education and communication are needed in the areas of:

- The importance of palliative care
- The value of participation in clinical trials

Both MBC patients and HCPs need to be educated about the importance of early access to and benefits of palliative care. Palliative care is considered standard of care and should be initiated early and individually managed according to where the patient is in his/her treatment journey[47,48].

Doctor/patient engagement needs to improve so that HCPs inform all cancer patients, particularly MBC patients, about clinical trials and the value of their participation in trials at all stages of treatment[13,49]. The National Comprehensive Cancer Network (NCCN) recommends clinical trial participation as part of optimal management of people living with cancer[50].

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