Metastatic Breast Cancer MBCalliance
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Breast Cancer Brain Metastasis (BCBM) Initiative: The Marina Kaplan Project

Executive Summary

A diagnosis of central nervous system (CNS) metastasis of the brain, or the linings of the brain and spinal cord known as leptomeningeal disease (LMD), has a worse prognosis and lower overall survival compared to patients with metastases in other organs. Incidence of brain metastasis is expected to increase, and with a disproportionate treatment response and debilitating side effects from the limited treatment options available, a patient-led initiative to address the lack of research in breast cancer brain metastasis (BCBM) and LMD is urgently needed.

The Breast Cancer Brain Metastasis (BCBM) Initiative: The Marina Kaplan Project launched in June 2020 as an official project of the Metastatic Breast Cancer Alliance which includes 32 nonprofits, 14 industry partners, and 30 individual patient advocates. The vision of the Alliance to improve the lives of those living with metastatic breast cancer (MBC) closely aligns with the goals of the Marina Project to address the unmet needs of breast cancer patients living with CNS metastasis. The overarching goal of the Marina Project is to accelerate evidence-based BCBM- and LMD-specific research through increased funding and by influencing key stakeholders.

The project is named in memory of Marina Kaplan, a brilliant epidemiologist and powerful advocate who was diagnosed with metastatic triple negative breast cancer in December 2013. After surviving 5 years with an aggressive MBC diagnosis and enduring multiple lines of treatment including several clinical trials, she developed brain metastasis in the last year of her life. Despite her best efforts, the restrictive eligibility criteria prevented her from participating in any further studies and she died of liver failure from MBC on January 13, 2020.

Marina was an active member of the MBC Alliance and the inspiration for this initiative. The Marina Project is driven by patients who represent a variety of demographics that reflect the diversity of the MBC community. The project has grown to include 27 members with representation from industry, research organizations, and individual patients. Nearly half the group is comprised of patients living with brain metastases or LMD.

Subcommittee Members

Christine Hodgdon (Lead), Jennifer Alderman, Laurie Campbell (MBC Alliance), Gissoo DeCotiis (Daiichi Sankyo), Elizabeth Frank, Flori Hendron, Lianne Kraemer, Ginny Mason (Inflammatory Breast Cancer Research Foundation), Julia Maués, Kristin Olson (Seattle Genetics), Chawnté Randall, Keyla Reece, Lynda Weatherby

Incidence of Brain Metastasis

Brain metastasis can present as a single tumor or multiple tumors, and it refers to a cancer that begins elsewhere in the body, but has spread to the brain.[1] The majority of brain metastases originate from primary cancers in the lung (40-50%), breast (15-25%), or from melanoma (5-20%)[5].

In the United States, approximately 70,000 patients living with cancer are diagnosed with brain metastases[12]. Other estimates are as high as 200,000 new cases of brain metastases diagnosed each year in the United States[6].

Across all breast cancer subtypes, approximately 10% to 15% of women with metastatic breast cancer develop brain metastases[13]. This rate is as high as 30% for women with advanced human epidermal growth factor receptor 2 (HER2)-positive disease, and as high as 50% for women with metastatic triple-negative breast cancer (TNBC)[4].

Though incidence of brain metastasis is difficult to assess, we can expect the frequency of brain metastasis to increase[6] for several reasons including 1) improved systemic therapy that lengthen the survival of patients with metastases to other organs[8], 2) improved imaging modalities and earlier detection, and 3) longer survival after a primary cancer diagnosis (e.g., patients with HER2+ breast cancer)[5].

Prognosis & Quality of Life Following A BCBM Diagnosis

Standard of care for brain metastases includes stereotactic radiation therapy for a lower number of lesions (typically 1-10), whole brain radiation therapy for a larger number of lesions or repeated needs for therapy, surgery for a low number of lesions in accessible locations and steroids for edema. Until recently, the only commercially available systemic treatments for BCBM patients included chemotherapy and anti-HER2 inhibitors (i.e., lapatinib and neratinib in combination with capecitabine) for HER2+ patients, and endocrine therapy and anti-CDK4/6 inhibitors for hormone receptor positive breast cancer patients. In April 2020, based on results of the HER2CLIMB trial, the FDA approved Tukysa (tucatinib) in combination with Herceptin (trastuzumab) and Xeloda (capecitabine) for the treatment of patients with metastatic HER2+ breast cancer. Tukysa is the first ever FDA approval in breast cancer that specifically noted the activity of the drug in patients with brain metastases.

Historically, the median survival of patients with BCBM was very poor, ranging from 3-6 months. However, with the advent of targeted treatments that effectively control extracranial disease, the overall survival for BCBM (all types combined) is now closer to just over 2 years, with a life expectancy of 3 years for those with HER2+ tumors[13]. While overall survival is significantly prolonged, retrospective studies report that up to 50% of HER2-positive patients died of cerebral progression[13].

Survival figures do not adequately describe the impact of brain metastases. Both the lesions and their treatments cause adverse effects ranging from seizures, loss of use of limbs, speech etc., and substantial neurocognitive declines. In particular, whole brain radiation therapy causes a longer term, irreversible severe cognitive decline in a proportion of patients, to the point where normal functions and family relationships are impossible.

Part of what contributes to such a dismal prognosis after a breast cancer patient is diagnosed with brain metastasis is due to major impediments in discovering and testing treatment options. These impediments are multiple and include:

- a poor understanding of the unique nature of the brain and its biological mechanisms[7]. What has been established to date is that brain metastases harbor mutations and other genetic modifications distinct from the primary breast tumor[3]. Also, breast tumor cells interact with multiple cells in the brain microenvironment to facilitate their colonization.

- the absence of sufficient pre-clinical *in vivo* animal models that mimic multiple aspects of brain metastasis in a clinical setting[5],
- the inability of many anticancer agents to cross either the blood-brain or blood-tumor barrier, and
- the lack of representation of patients with brain metastasis in clinical trials due to restrictive eligibility criteria[5]. A survey of physicians found that 66% had patients excluded from clinical trials due to brain metastases[14]. Furthermore, less than 3% of clinical trials require CNS disease, and only 1% of all clinical trials were designed specifically for BCBM patients. Of the clinical trials that do assess CNS disease, these trials lack appropriate endpoints; Neurologic function, quality of life, local control, cognitive benefit are examples of what should be primary endpoints in clinical trials for patients with brain metastases.

Disparities in the BCBM Community

The disparities in the quality of healthcare within the BCBM community are even greater among patients of African American race, Hispanic ethnicity, and low socioeconomic status [11]. Though research is lacking, studies have shown that patients of black race or Hispanic ethnicity were less likely to be treated with stereotactic radiosurgery, and utilization of this modality was also lower among patients with Medicare, Medicaid, or no insurance[7]. Outcomes following a craniotomy for brain metastases varied greatly with black patients having a significantly higher morbidity, almost twice the mortality, higher complication rates, and longer hospital stays compared with white/other women[10]. There is even some evidence that like TNBC, the occurrence of breast cancer patients diagnosed with brain metastases is higher among African Americans compared to other racial groups[2].

Leptomeningeal Metastases

Leptomeningeal disease (LMD) is spread of the tumor growth to the linings of the brain or in the CSF that bathes the brain and spinal cord. Patients with the rarer occurrence of leptomeningeal disease (LMD) suffer an even worse prognosis, more limited treatment options, and represent a seriously underserved population of patients. The average time from diagnosis to death following an LMD diagnosis is 3.5 months, and only 12 LMD-specific clinical trials exist globally as of August 2019.

Objectives & Vision

This initiative is a project of the MBC Alliance driven by patients who represent a variety of demographics that reflect the diversity of the MBC community. Not all participants have a BCBM or LMD diagnosis, but all are committed to addressing disparities within the BCBM and LMD communities by removing barriers to access clinical trials and novel treatments.

The overarching goal of this initiative is to **accelerate evidence-based BCBM- and LMD-specific research through increased funding and by influencing key stakeholders** to 1) increase the quality of basic science research, 2) increase the number of clinical trials testing a variety of interventions, 3) ensure an inclusive clinical trial design with less restrictive eligibility criteria, and 4) incorporate clinically meaningful trial endpoints that measure *both* quality of life and survival for patients living with BCBM or LMD.

By achieving the aforementioned goals, this initiative has the potential to increase and improve research for *all* cancer patients which may lead to 1) novel FDA-approved treatments and therapies; 2) standardized guidelines for diagnosis, treatment, and monitoring; and 3) remarkable improvements in the lives and outcomes for all patients living with CNS metastasis.

Furthermore, this initiative will highlight the importance of **recognizing patients as key *partners* in the research process** by building a coalition of patient advocates who can 1) advise researchers on clinical trial design that ensures both patient accrual and retention in clinical trials, and 2) assist with clinical trial recruitment by disseminating trial information through our extensive network of patients.

Goals of Initiative *

Goals have been reviewed by over a dozen experts in the field. See addendum for list of advisory board members.

This initiative aims to broaden the scope and breadth of BCBM and LMD research by addressing gaps in the translational discovery spectrum from fundamental science to its implementation in clinical trials through achievement of the following goals:

1. Improve the quality of basic research for CNS metastasis including:
    - Pre-clinical in vivo animal models that more accurately and effectively mimic brain metastasis in a clinical setting, especially immunocompetent models (e.g., syngeneic models or mice with humanized immune systems)
    - Use of both in vivo and ex vivo models (organoids) to study how the microenvironment promotes or inhibits tumor growth
    - Molecular characterization of more tumors and cell lines
    - Use of cell lines and patient derived tissues of *all* breast cancer subtypes including HR+ which is typically excluded in BCBM and/or LMD pre-clinical research
    - Identifying overarching interactions between tumor cells and the brain and leptomeningeal microenvironment that can be therapeutically targeted
    - Understanding the potential contribution of the immune system to brain metastasis treatment
2. Increase the number of clinical trials in the following areas where CNS metastasis research is lacking including:
    - Anticancer agents that cross either the blood-brain or blood-tumor barrier
    - Novel delivery systems that combine drugs with other molecules that can penetrate the brain
    - Genomic profiling of the brain to answer the following questions: 1) Is the mutation profile of brain metastases different from other metastases? 2) Are there actionable mutations we can target with existing therapies? 3) Can we identify genomic predictors of brain metastases in breast cancer?
    - Trials with new approaches such as biopsy driven trials, and prevention of additional brain metastases after initial treatment

- Blood-based and cerebrospinal fluid-based biomarkers (e.g., circulating DNA and circulating tumor cells) which can be used as both prognostic and predictive markers in patients with BCBM and/or LMD
- Brain imaging to determine who is more likely to relapse in the brain and if earlier detection of brain metastases before the onset of symptoms will improve clinical outcomes for the following patients: 1) *de novo* metastatic, 2) metastatic without brain involvement, and 3) high risk early stage patients
- Studies that target patients with brain metastasis only (i.e., controlled systemic disease) for investigation. Could we give this subset of patients additional interventions like small molecule inhibitors (e.g., tyrosine-kinase) to decrease their chance of relapse?

3. Diversify the type of interventions tested in clinical trials including:
    - Drugs/biologics – including immunotherapy
    - Novel delivery systems (e.g., intrathecal)
    - Imaging techniques
    - Radiation
    - Surgery – including laser interstitial thermal therapy (LITT)
4. Eliminate broad exclusions and restrictive eligibility criteria in new or existing clinical trials including:
    - Patients with untreated or progressing brain metastases
    - Patients with leptomeningeal disease
    - Patients with brain lesions smaller than 1cm (e.g., Patients with a contrast-enhancing lesion that is at least 5 mm and can be accurately measured in at least one dimension are considered measurable[9] and should not be excluded.)
5. Standardize the following patient cohorts for advanced solid tumor and/or CNS metastasis-specific clinical trials:
    - Treated or stable brain metastases
    - Untreated brain metastases
    - Progressing brain metastases
    - Leptomeningeal disease
    - All breast cancer subtypes including HR+
6. Improve the quality of BCBM- and LMD-specific clinical research through the adoption and incorporation of clinically meaningful trial endpoints that measure both survival and quality of life including the following:
    - Overall survival (OS)
    - Progression-free survival (PFS)
    - Central nervous system progression-free survival (CNS-PFS)
    - Intracranial overall response rate (ORR-IC)

- Intracranial duration of response (DOR-IC)
- Time from initial brain metastasis to subsequent brain lesions
- Time to treatment/protocol change (i.e., whole brain radiation therapy, surgery, etc.)
- Neurologic function
- Local control

PRO-CTCAE[1] Endpoints:

- Physical function
- Emotional function
- Treatment tolerability
- Cognitive benefit (e.g., HVLT-R[2])
- Health-related Quality of Life (HRQOL)
- Depression/fatigue
- Financial toxicity

[1] Patient Reported Outcomes - Common Terminology Criteria for Adverse Events

[2] HVLT-R: Hopkins Verbal Learning Test - Revised for Total Recall, Delayed Recall, Delayed Recognition, & Trail Making Tests

Advisory Board Members

Profession	Name	Institution	Location
BC Onc	Dr. Carey Anders, MD	Duke University	Durham, NC
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BC Onc	Dr. Erika Hamilton, MD	Sarah Cannon Research Institute	Nashville, TN
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Researcher	Dr. Josh Neman-Ebrahim, PhD	University of Southern California	Los Angeles, CA
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Researcher	Dr. Patricia Steeg, PhD	National Institutes of Health (NIH)	Bethesda, MD
BC Onc	Dr. Alexandra Zimmer, MD	National Institutes of Health (NIH)	Bethesda, MD

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