Modeling the Patterns of Breast Cancer Early Metastases

UFHCC Gainesville and Univ. of Miami Sylvester CCC

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Breast cancer mets statistics

- In 2016, > 230,000 women in the US will be diagnosed with invasive breast cancer.
- Approximately 11% (26,000) of these will develop distant metastases after an initial diagnosis of no metastases.

  = our target patients

- These will account for nearly 2/3 of the total number (40,000) of breast cancer deaths annually.

Breast cancer mets management

- Current National Cancer Care Network (NCCN) guidelines for asymptomatic breast cancer survivors omit proactive imaging for the detection of early-stage metastatic disease, regardless of a patient's metastatic risk.

- The presentation of an outward symptom (persistent cough, bone pain, headaches or dizziness, or abnormal laboratory findings), is typically associated with advanced metastatic disease -- multiple large masses afflicting multiple organs.

- Currently, metastatic breast cancer (MBC) carries a dismal 20% overall survival (OS) and 2% disease-free survival (DFS) at 5 years.

Limited efficacy of chemotherapy in recurrence

- The NCCN guidelines are based on 2 surveillance imaging studies performed in Italy from 1985-1993 where additional chemotherapy was the only treatment option (pre-dated image-guided surgery and SRT). Early detection and treatment did not prolong 5-year OS in the women who developed BC metastases.

Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. The GIVIO Investigators, JAMA, vol. 271, no. 20, pp. 1587–1592, May 1994.

- SWOG Protocol S0500 (2014): Additional systemic therapy did not improve OS for patients with persistent metastatic breast cancer after first line chemotherapy.

Smerage, et al., *Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500,* J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. **32**(31), 3483–3489 (2014)

Combined treatment Efficacy

Oligometastases (<=5 mets) treated using combined local + systemic therapy can achieve dramatically increased OS and DFS.

- UF/Univ. of Rochester (2011): 47% OS, 36% DFS at 8 years for Oligo-.

Milano M, Katz A, Zhang H, Okunieff P, *Oligometastases Treated With Stereotactic Body Radiotherapy: Long-Term Follow-Up of Prospective Study*, Int. J. Radiat. Oncol. Biol. Phys. (2011).

- UM (2010-2014): 80% vs 46% 5-year OS for oligo-/non-oligo.

Gajjar S, Yoga A, Reis I, Zeidan Y, Takita C, "Predictors of Outcomes in Breast Cancer Patients With Oligometastases," Proc. of the 97th Annual Meeting of the American Radium Society (2015)

- 48.5% 5-year OS for oligo-mets vs. 10.7% for non-oligo (1978-2005 data)

Jain S, Dorn P, Chmura S, Weichselbaum RR, Hasan Y, *Incidence and implications of oligometastatic breast cancer.*, J. Clin. Oncol. **30**(Suppl), abstr e11512 (2012).

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UNIVERSITY OF MIAMI HEALTH SYSTEM

IMAGING THE PATTERNS OF BREAST CANCER EARLY METASTASES:

Clinical Trial Update

Cristiane Takita, MD, MBA

FACCA Retreat, Coral Gables, FL

03/04/16

BreastMetsPats
Primary Objectives

1. To determine how many high-risk breast cancer patients have oligometastatic presentation under proactive imaging.

2. To measure the incidence of metastases, their number and size at first instance, time to first instance, growth rates and target organs to define the optimal surveillance imaging protocol.

3. To relate the features of metastatic presentation with primary tumor factors (size, stage, ER/PR/HER2) and patient-specific factors (age, race, BRCA gene status).

BreastMetsPats
Secondary Objectives

1. To measure the local control rate, acute and late side effects for ablative local therapy in an intensive surveillance regimen compared with previous findings.

2. For secondary instance of distant metastases, measure their incidence, their number and size at, time to instance, growth rates and target organs.

BreastMetsPats
Patient Selection

Eligibility

Female patients with breast cancer who have presented within the last 48 months with a diagnosis that associates them with high risk (>30%) for developing metastatic disease but who at the time of enrollment are not known to have metastatic disease. Patients meeting this criterion are those that have any of the following presentations:

1. hormone receptor (or triple) negative breast cancer with 3 or more positive axillary lymph nodes;
2. a Stage III diagnosis (T1, N2 or T3, N1 or T4 or N3);
3. a primary tumor >2 cm and positive axillary lymph nodes (T2, N2);
4. multiple primary tumors with cumulative volume >= that of a single 2; cm tumor, and positive axillary lymph nodes
5. any number of lymph nodes with extranodal extension;
6. any internal mammary or supraclavicular nodes (N3);
7. any primary tumor that has grown into the chest wall or skin (T4);
8. or inflammatory breast cancer

BreastMetsPats Subject Involvement

1. All enrolled subjects will under go a single body PET/CT scan that includes a diagnostic-quality CT scan with contrast acquired in the same imaging session; and a single brain MRI scan with contrast to be completed in separate imaging session but within 2 weeks of the PET/CT scan. Imaging will take place within 7 months after enrollment.

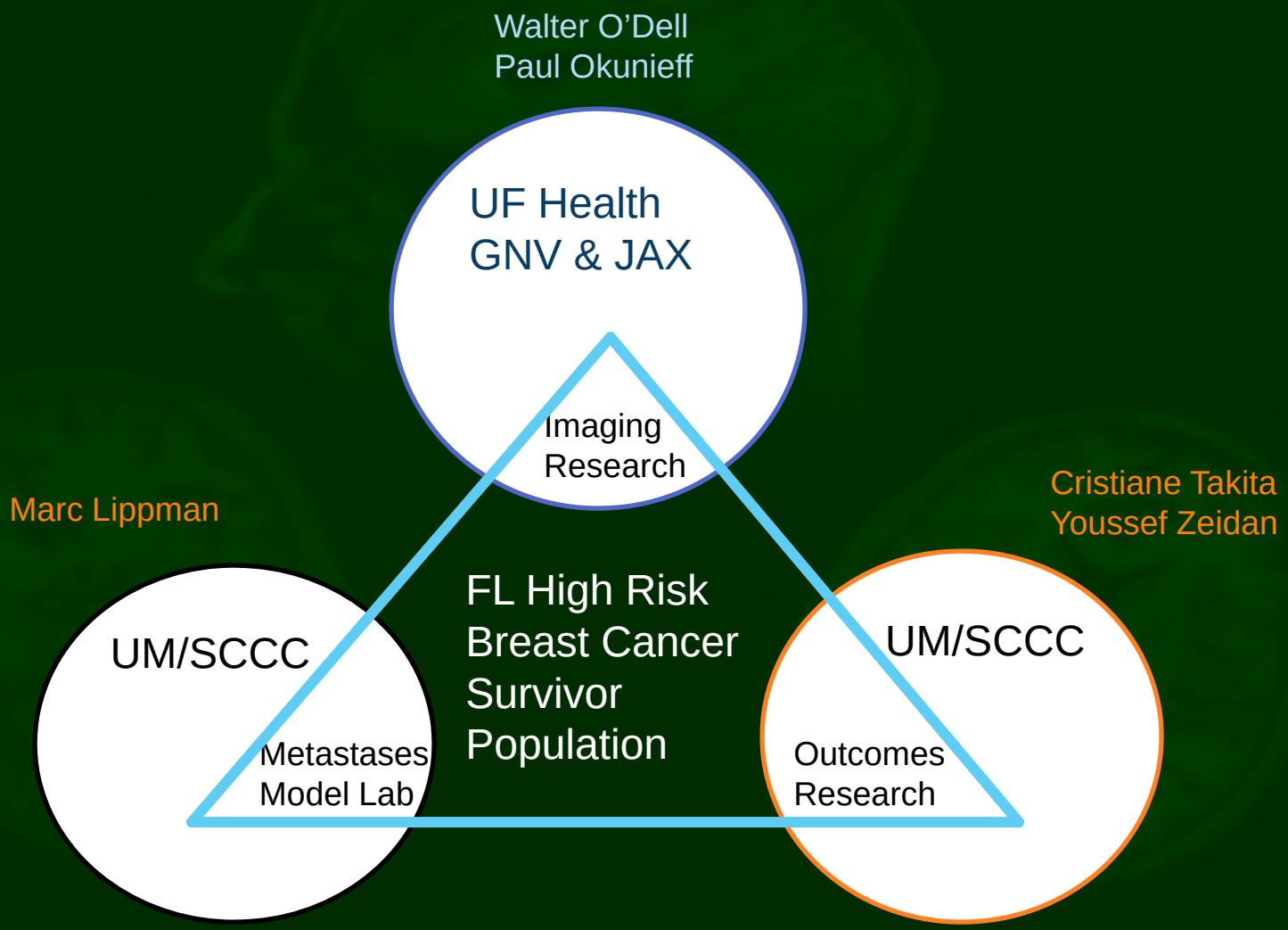
2. Medical records related to their cancer and care will be monitored for the duration of the patient's life.

Clinical Trial Update

- **Timeline:**
  - **7/13/15: FACCA award starting date ($50,000)**
  - **9/3/2015: Protocol submission to UFHCC PRMC**
  - **9/29/2015 UF PRMC letter of approval**
  - **10/23/15: Submission to UM/SCCC PRC for expedited review**
  - **10/26/15: UM/SCCC PRC letter of approval**
  - **11/4/15: Protocol submission to UM/SCCC IRB**
  - **2/1/16: UM IRB letter of approval**
  - **1/29/2015: Protocol submission to UF IRB**
  - **2/1/16: 1st Site initiation visit for coordinators**
  - **2/22/16: Short version of Spanish ICF approved by IRB**
  - **As of 2/29/16: 2 UM patients accrued, 1 patient screened**
  - **3/2/16: UF IRB review**

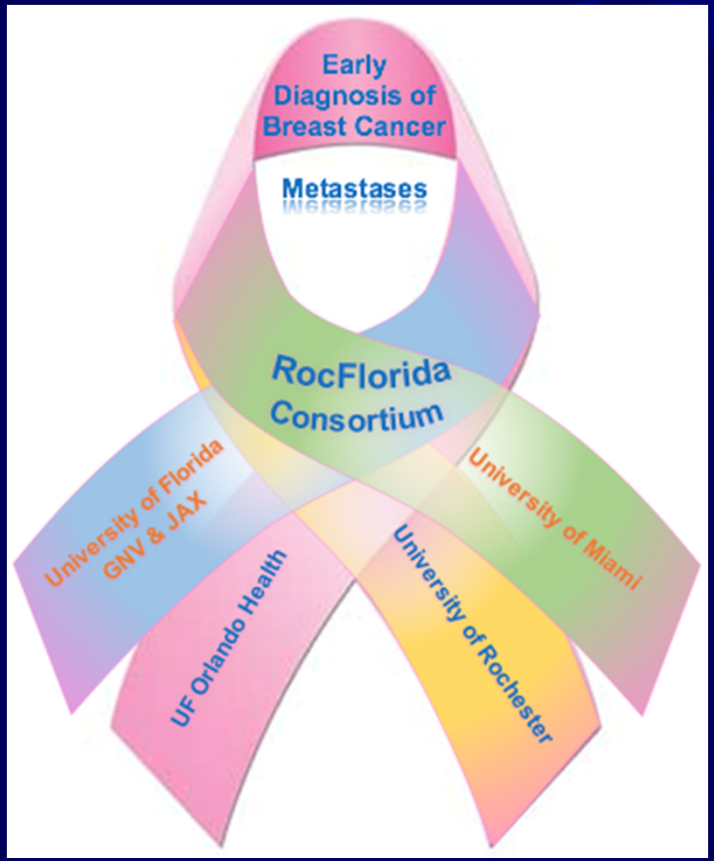
  - **Goal is to complete accrual by end of grant cycle**

Active Surveillance in High Risk Breast Cancer



Future Funding Plans: DOD BCR

Imaging and modeling the initial spread of metastases in breast cancer
PIs: Lippman/Takita (UM), Milano (URMC), O'Dell (UFHCC)



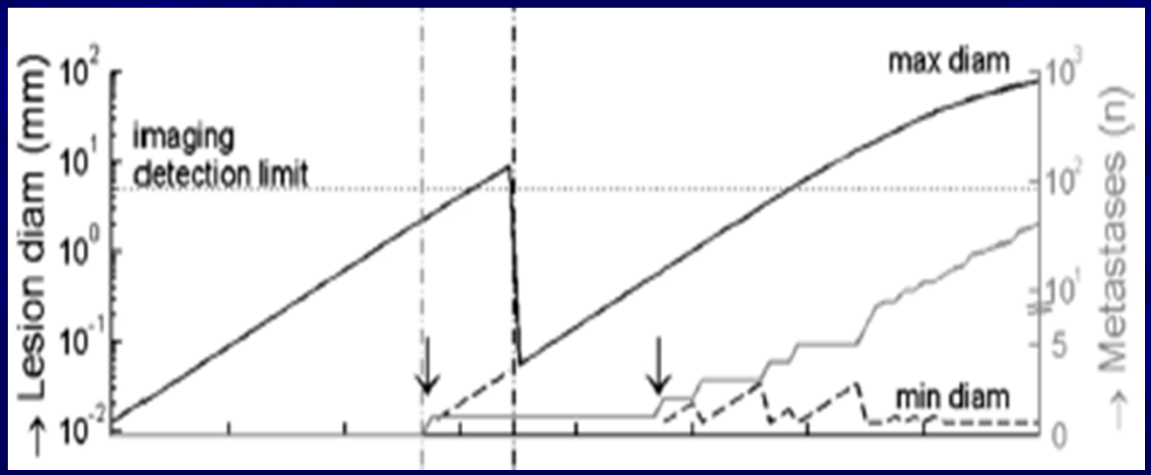
"Through this work we will forge a direct path through the NRG and RTOG for a national clinical trial to evaluate the benefit of combining proactive imaging with targeted therapy of breast cancer metastases."

Future Funding Plans: DOD BCR

Aim 1. Prospectively measure patterns of first incidence of breast cancer metastasis.

Aim 2. Retrospectively measure patterns of metastasis presentation in breast cancer patients.

Aim 3. Model the dissemination of metastasis* to design optimal surveillance imaging protocol.



*Coumans F A, Siesling S, Terstappen LW, *Detection of cancer before distant metastasis*, BMC Cancer **13**, 283 (2013).

DOD BCR

Original submission (4/2015): 3-yr, 2 institutions (UF+UM), $1M direct
Scored: 2.5 (good)
"This was a controversial review, and agreement on potential impact could not be achieved. After a lengthy panel discussion, some panel members continued to express high enthusiasm, but many agreed that the identified weaknesses related to impact raised significant concerns that diminished enthusiasm."

Planned resubmission (4/2016) 5-years, 3 institutions, $3.3M direct

Revisions: Yoke with but not overlap NRG-BR002: (opened Dec. 2014)

A Phase IIR/III Trial of Standard of Care Therapy With or Without Stereotactic Body Radiotherapy (SBRT) and/or Surgical Ablation for Newly Oligometastatic Breast Cancer

Future Funding Plans: NIH NCI R01

Pathway to a national trial of surveillance for metastases in breast cancer survivors.

PIs: Lippman (UM), Milano (URMC), O'Dell (UFHCC)

Planned submission: June 5, 2016

Aim 1. Prospectively measure patterns of breast cancer metastasis to design optimal surveillance imaging protocol.

Aim 2. Quantify the time-course of circulating tumor cells (CTCs) and additional blood markers to identify patients most likely to benefit from intensive surveillance and aggressive treatment.

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Questions

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Thanks again for your continued support