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TITLE: Could HER2 Heterogeneity Open New Therapeutic Options in Patients with HER2- Primary Breast Cancer?

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14. ABSTRACT The purpose of this study is to determine if targeted imaging with a HER2 targeting PET tracer can detect HER2-positive metastases in patients with HER2-negative primary breast cancer. An initial nine patients have completed the trial. Five patients demonstrated suspicious foci on ⁸⁹ Zr-trastuzumab PET/CT. Two of five patients with suspicious foci had biopsy proven HER2-positive metastases. In this early stage clinical trial, ⁸⁹ Zr-trastuzumab PET/CT may detect HER2-positive metastases in patients with HER2-negative primary breast cancer. This is an initial proof-of-concept that targeted imaging may help identify patients eligible for targeted therapies. The problem of false positive results will need to be addressed.					
15. SUBJECT TERMS Breast cancer, HER2, tumor heterogeneity, PET/CT, ⁸⁹ Zr-trastuzumab					
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1. INTRODUCTION:

Human epidermal growth factor receptor 2 (HER2) is a highly valuable biomarker in breast cancer, and its expression directly influences treatment. Growing evidence suggests that HER2 expression may change between the primary breast malignancy and metastases. This is an example of tumor heterogeneity. Inaccurate knowledge of receptor status in metastases due to tumor heterogeneity may lead to suboptimal treatment of metastatic breast cancer.

Our central hypothesis is that imaging with a targeted HER2 radiotracer will allow us to identify patients with HER2-negative primary breast cancers who develop HER2-positive metastases, and who may benefit from the addition of HER2 therapy.

2. KEYWORDS:

Breast cancer

Human epidermal growth factor receptor 2 (HER2)

Tumor heterogeneity

PET/CT

Targeted imaging

⁸⁹Zr-trastuzumab

3. ACCOMPLISHMENTS:

- **What were the major goals of the project?**
 - Determine the proportion of patients with HER2-negative primary breast cancer who develop imagable HER2-positive metastases using a targeted HER2 radiotracer (Specific Aim #1)
 - Among patients with HER2-positive metastases discovered in Specific Aim #1, determine if HER2-targeted therapy results in a measurable treatment response (Specific Aim #2)
- **What was accomplished under these goals?**
 - IND for ⁸⁹Zr-trastuzumab and IRB for study protocol were completed and maintained.
 - The purpose of this trial is to determine if targeted imaging with a HER2-targeting PET tracer can detect HER2-positive metastases in patients with HER2-negative primary breast cancer. Patients with HER2-negative primary breast cancer and evidence of distant metastases were enrolled in an IRB-approved prospective clinical trial. Archived pathology from the patient's primary breast cancer was retested to confirm HER2-negative disease. Patients with confirmed HER2-negative primary breast cancer underwent ⁸⁹Zr-trastuzumab PET/CT to screen for foci suspicious for HER2-positive metastases. Suspicious foci imaged on ⁸⁹Zr-trastuzumab PET/CT were pathologically examined to define HER2 status. Patients with pathologically proven HER2-positive metastases underwent HER2-targeted therapy to evaluate treatment response. An initial nine patients have completed the trial. All nine had pathologic retesting that confirmed HER2-

negative primary breast cancer. Five demonstrated suspicious foci on ^{89}Zr -trastuzumab PET/CT. Of the five with suspicious foci, two had biopsy-proven HER2-positive metastases. These two received HER2-targeted therapy, with one demonstrating response. In this early-stage clinical trial, ^{89}Zr -trastuzumab PET/CT may detect HER2-positive metastases in patients with HER2-negative primary breast cancer. This is an initial proof-of-concept study, demonstrating that targeted imaging may help identify patients eligible for targeted therapies.

- 41 more patients will be recruited in the trial over the next 27 months.

- **What opportunities for training and professional development has the project provided?**

- Nothing to Report

- **How were the results disseminated to communities of interest?**

- The first manuscript for this project is currently being drafted to report the initial findings.

- **What do you plan to do during the next reporting period to accomplish the goals?**

- Increased accrual will be needed to reach our goal of 50 patients over 3 years. We initially anticipated 14 patients would be accrued in the first year and 18 patients would be accrued in each of the following 2 years. We are slightly behind our first-year goal (9 patients in 10 months). We anticipate that accrual will increase as the initial successful results are communicated.

4. IMPACT:

- **What was the impact on the development of the principal discipline(s) of the project?**

- The initial results already demonstrate the proof of concept that targeted imaging can be used to help identify patients eligible for targeted therapies.

- **What was the impact on other disciplines?**

- The initial results confirm that there may be heterogeneity of HER2 expression between the primary malignancy and distant metastases. This adds to the growing knowledge of tumor heterogeneity.

- **What was the impact on technology transfer?**
 - Nothing to Report.
- **What was the impact on society beyond science and technology?**
 - Nothing to Report.

5. CHANGES/PROBLEMS:

The detection of ^{89}Zr -trastuzumab foci that represent HER2-negative (rather than HER2-positive) metastatic breast cancer is considered a problem. There have been three such patients. At the current time, there will be no changes in the conduct of the protocol as the numbers are still too low to fully understand the problem. This problem will be re-addressed after further recruitment to determine if this requires alteration of the conduct of the protocol.

- **Changes in approach and reasons for change**
 - Nothing to Report.
- **Actual or anticipated problems or delays and actions or plans to resolve them**
 - Nothing to Report.
- **Changes that had a significant impact on expenditures**
 - Nothing to Report.
- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
 - Nothing to Report.
- **Significant changes in use or care of human subjects**
 - Nothing to Report.
- **Significant changes in use or care of vertebrate animals.**
 - Nothing to Report.
- **Significant changes in use of biohazards and/or select agents**
 - Nothing to Report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**
 - **Journal publications.**
 - Nothing to currently report. The first manuscript for this project is currently being drafted to report the initial findings. The DoD will be acknowledged in this manuscript.

- **Books or other non-periodical, one-time publications.**
 - Nothing to Report.

- **Other publications, conference papers, and presentations.**
 - Nothing to Report.

- **Website(s) or other Internet site(s)**
 - Nothing to Report.

- **Technologies or techniques**
 - Nothing to Report.

- **Inventions, patent applications, and/or licenses**
 - Nothing to Report.

- **Other Products**
 - Nothing to Report.

- **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**
- **What individuals have worked on the project?**
 - *Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."*

Name:	Gary Ulaner
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	

Nearest person month worked:	3
Contribution to Project:	Protocol design; patient recruitment; reviewing pathologic results, performance and interpretation of ⁸⁹ Zr-trastuzumab PET/CT scans; selection of biopsy targets; data collection
Funding Support:	Support outside of DoD grant comes from a Komen Foundation Grant and salary from Memorial Sloan Kettering Cancer Center.

Name:	Hanh Pham
Project Role:	Research Assistant
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	Preparation and filing of paperwork; scheduling patients for exams and appointments; ensuring project compliance; data collection entry, reporting, and regulatory monitoring
Funding Support:	Support outside of DoD grant comes from salary from Memorial Sloan Kettering Cancer Center.

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
 - Nothing to Report
- **What other organizations were involved as partners?**
 - Nothing to Report

7. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:** *Not applicable*
- **QUAD CHARTS:** *Not applicable.*

8. APPENDICES: *None.*

***** **ADDITIONAL NOTES:**

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