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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. Twenty-three patients have been accrued to the trial. Nine patients demonstrated suspicious foci on ^{89}Zr-trastuzumab PET/CT. Two of nine patients with suspicious foci had biopsy-proven HER2-positive metastases. Thus, ^{89}Zr-trastuzumab PET/CT may detect HER2-positive metastases in patients with presumed HER2-negtive primary breast cancer. This is an initial proof-of-concept that targeted imaging may help identify patients eligible for targeted therapies. However, false-positive results limit the ability of ^{89}Zr-trastuzumab to be translated into clinical use, and a more specific radiotracer will be needed.

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
^{89}Zr-trastuzumab

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Task 1. Submission and approval of regulatory documents
1a. IND for ^{89}Zr-trastuzumab
1b. IRB Protocol

Task 2. Determine the proportion of patients with HER2- primary breast cancer who develop imagable HER2+ metastases using a targeted HER2 radiotracer (Specific Aim #1)
2a. Accrue 50 patients at a rate of 1-2 per month
2b. Confirm HER2- status of archived pathology tissue samples
2c. ^{89}Zr-trastuzumab PET/CT to identify patients suspicious for HER2+ metastases
2d. Biopsies to confirm HER2+ malignancy
2e. Interim statistical analyses as predefined accrual numbers are met

Task 3. Among patients with HER2+ metastases discovered in Specific Aim #1, determine if HER2-targeted therapy results in a measurable treatment response (Specific Aim #2)
3a. Pre-treatment baseline disease assessments with FDG PET and CT
3b. HER2-targeted systemic therapy
3c. Post-treatment disease assessments with FDG PET and CT
3d. Final statistical analyses

What was accomplished under these goals?

Task 1. Submission and approval of regulatory documents

1a. IND for ^{89}Zr-trastuzumab

IND for ^{89}Zr was completed and maintained

1b. IRB Protocol

IRB for study protocol was completed and maintained.

Task 2. Determine the proportion of patients with HER2- primary breast cancer who develop imagable HER2+ metastases using a targeted HER2 radiotracer

2a. Accrue 50 patients at a rate of 1-2 per month
23 patients were accrued to the protocol as of 30-Sep-2016.

2b. Confirm HER2- status of archived pathology tissue samples
HER2- status of archived pathology samples was confirmed for all patients.

2c. ^{89}Zr-trastuzumab PET/CT to identify patients suspicious for HER2+ metastases
^{89}Zr-trastuzumab PET/CT was performed in all patients. Nine patients had ^{89}Zr-trastuzumab foci suspicious for HER2+ disease.

2d. Biopsies to confirm HER2+ malignancy
Biopsies were performed in all nine patients with ^{89}Zr-trastuzumab foci suspicious for HER2+ disease.

- Two of nine were positive for HER2+ disease on pathology (true positives)
- Seven of nine were not positive for HER2+ disease on pathology (false positives)

2e. Interim statistical analyses as predefined accrual numbers are met
Interim statistical analyses were performed.

Task 3. Among patients with HER2+ metastases discovered in Specific Aim #1, determine if HER2-targeted therapy results in a measurable treatment response

3a. Pre-treatment baseline disease assessments with FDG PET and CT
Pre-treatment baseline disease assessments were performed in the two patients with biopsy-proven, HER2+ metastases.

3b. HER2-targeted systemic therapy
HER2-targeted systemic therapy was performed in the two patients with biopsy-proven, HER2+ metastases.

3c. Post-treatment disease assessments with FDG PET and CT

Post-treatment disease assessments were performed in the two patients with biopsy-proven, HER2+ metastases. Both patients demonstrated response to HER2-targeted therapy (one complete, one partial).

3d. Final statistical analyses

Final statistical analyses are pending.

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 has been published:

  Detection of HER2-positive metastases in patients with HER2-negative primary breast cancer using the ^{89}Zr-DFO-trastuzumab PET/CT. Ulaner et al, Journal of Nuclear Medicine 2016, e-published ahead of print, PMID: 27151988

  The first presentation for the project has been made:

  Detection of HER2-positive metastases in patients with HER2-negative primary breast cancer using ^{89}Zr-DFO-trastuzumab, Ulaner et al, Annual Meeting of the Society of Nuclear Medicine and Molecular Imaging, San Diego, California, June 2016.

- **What do you plan to do during the next reporting period to accomplish the goals?**
  - The objective of the study (detection of HER2+ metastases in patients with presumed HER2- disease) has been accomplished. This is a proof-of-concept that targeted imaging may help identify patients eligible for targeted therapies. However, the high rate of false positives limits the usefulness of ^{89}Zr-trastuzumab to be translated to the clinic. A more specific radiotracer will be needed. We have spoken with our DoD Science officer, Julia M. Huiberts, and have come up with a plan to obtain an Investigational New Drug (IND) application from the Food and Drug Administration (FDA) for a potentially more specific HER2-targeting PET radiotracer, ^{89}Zr-pertuzumab, and perform the remainder of this trial with ^{89}Zr-pertuzumab. This will delay the completion of the study by the time it takes to obtain the ^{89}Zr-pertuzumab IND from the FDA (estimated to be one year); however, this change may increase the specificity of our HER2-targeted imaging.

4. **IMPACT:**
   - **What was the impact on the development of the principal discipline(s) of the project?**
     - The 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- (rather than HER2+) metastatic breast cancer is considered a problem. As previously mentioned, we have spoken with our DoD Science officer, Julia M. Huiberts, and have come up with a plan to obtain an IND application from the FDA for a potentially more specific HER2-targeting PET radiotracer, ^{89}Zr-pertuzumab, and perform the remainder of this trial with ^{89}Zr-pertuzumab. This will delay the completion of the study by the time it takes to obtain the ^{89}Zr-pertuzumab IND from the FDA (estimated to be one year); however, this change may increase the specificity of our HER2-targeted imaging.

   - **Changes in approach and reasons for change**
     - We will change from ^{89}Zr-trastuzumab to ^{89}Zr-pertuzumab imaging, a potentially more specific antibody conjugate, to attempt to increase specificity of HER2-targeted imaging.
   - **Actual or anticipated problems or delays and actions or plans to resolve them**
     - Use of ^{89}Zr-pertuzumab will require an IND application to the FDA. This will delay the completion of the study by the time it takes to obtain the ^{89}Zr-pertuzumab IND from the FDA (estimated to be one year).
   - **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.**

       Ulaner et al, Journal of Nuclear Medicine 2016, e-published ahead of print, PMID: 27151988

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

     - **Other publications, conference papers, and presentations.**

       Detection of HER2-positive metastases in patients with HER2-negative primary breast cancer using ^{89}Zr-DFO-trastuzumab, Ulaner et al., Annual Meeting of the Society of Nuclear Medicine and Molecular Imaging, San Diego, California, June 2016

     - **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 (PI): No change

Name:	Hanh Pham (Research Assistant): No change

- **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.*

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********** **ADDITIONAL NOTES:** n/a