

**A Phase 2 study of [<sup>18</sup>F]fluoroestradiol positron emission tomography (FES-PET) as a marker of hormone sensitivity in metastatic breast cancer (MBC).**

**Molecular Imaging and Biology**

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Journal: Molecular Imaging & Biology

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Appendix Table 1: Patient outcomes (sorted by increasing average FES SUV dynamic)

| Index - id | age | yrs since primary | # lesions (sweep) | # lesions (dynamic) | Prior endocrine therapy | ER of metastatic biopsy | Any qual. FES negative sites? | Avg FES SUV (dyn) | Geometric mean SUV (sweep, 3 highest FDG) | Average sqrt of FES/FDG (sweep, 3 lowest ratio) | Study treatment              | response  |
|------------|-----|-------------------|-------------------|---------------------|-------------------------|-------------------------|-------------------------------|-------------------|---|---|------------------------------|---|
| 1-013      | 67  | 3                 | 1                 | 1                   | AI                      | Positive                | Yes                           | 0.6               | 0.9                                       | 0.3   | tamoxifen                    | PD  |
| 2-016      | 69  | 20                | 2                 | 2                   | AI                      | Negative                | Yes                           | 0.7               | 0.9                                       | 0.7   | tamoxifen                    | NA (discontinued after biopsy)                                |
| 3-001      | 60  | 7                 | 5                 | 5                   | AI                      | Negative                | Yes                           | 0.8               | 0.4                                       | 0.4   | tamoxifen                    | PD  |
| 4-014      | 58  | 10                | 8                 | 3                   | AI, Tam                 | Negative                | Yes                           | 1.0               | 0.7                                       | 0.5   |                              | NA (chemotherapy)   |
| 5-011      | 48  | 1                 | 12                | 4                   | None                    | Positive                | Yes                           | 1.1               | 0.8                                       | 0.3   |                              | NA (hospitalized soon after scan, never on endocrine therapy) |
| 6-018      | 57  | 0                 | 4                 | 2                   | None                    | Weakly Positive         | No                            | 1.6               | 1.5                                       | 1.1   | anastrozole                  | PD  |
| 7-010      | 75  | 9                 | 8                 | 3                   | AI, Tam                 |                         | No                            | 1.7               | 2.2                                       | 0.5   | letrozole                    | PR  |
| 8-003      | 39  | 0                 | 9                 | 3                   | None                    | Weakly Positive         | No                            | 1.7               | 2.2                                       | 0.7   | OS + letrozole + fulvestrant | PR  |
| 9-017      | 63  | 0                 | 12                | 2                   | None                    | Positive                | No                            | 1.9               | 4.3                                       | 0.7   | anastrozole                  | NA (surgical AE @ 2 days on AI)                               |
| 10-015     | 64  | 0                 | 4                 | 2                   | None                    | Positive                | Yes                           | 2.0               | 1.3                                       | 0.8   | letrozole                    | SD  |
| 11-019     | 77  | 24                | 7                 | 4                   | Tam                     | Positive                | No                            | 2.1               | 1.6                                       | 0.6   | anastrozole                  | PD  |
| 12-020     | 45  | 3                 | 2                 | 2                   | AI                      | Positive                | No                            | 2.6               | 2.8                                       | 1.0   | fulvestrant                  | PR  |
| 13-008     | 42  | 3                 | 4                 | 1                   | AI                      | Positive                | No                            | 2.9               | 2.6                                       | 0.9   | exemestane + fulvestrant     | PD  |
| 14-006     | 65  | 0                 | 6                 | 4                   | None                    |                         | No                            | 3.0               | 3.1                                       | 0.7   | letrozole                    | PR  |
| 15-002     | 62  | 4                 | 11                | 5                   | AI                      | Positive                | No                            | 3.3               | 3.7                                       | 0.9   | tamoxifen                    | PD  |
| 16-012     | 59  | 4                 | 11                | 3                   | None                    |                         | No                            | 3.3               | 3.5                                       | 0.8   | letrozole                    | PD  |
| 17-009     | 65  | 29                | 6                 | 4                   | None                    | Positive                | No                            | 3.5               | 4.1                                       | 0.9   | letrozole + fulvestrant      | SD  |
| 18-004     | 59  | 13                | 6                 | 3                   | Tam                     | Positive                | No                            | 5.1               | 4.5                                       | 1.5   | letrozole + fulvestrant      | SD  |
| 19-005     | 73  | 12                | 6                 | 3                   | None                    |                         | No                            | 5.9               | 6.5                                       | 1.3   | letrozole + fulvestrant      | SD  |

Abbreviations: AI=Aromatase Inhibitor, Tam=tamoxifen, OS=ovarian suppression, PD=progressive disease, PR=partial response, SD=stable disease, AE=adverse event

Appendix Table 2: Paired FES PET and biopsy results for the same lesion (with other lesions reported for comparison)

| Index-id | Biopsy procedure   | Days FES PET after biopsy | ER Allred  | Paired FES SUVmean(s) (dynamic field of view) | Paired FDG SUVmax | Paired FES SUVmean(s) (sweep) | Other lesions FES SUVmean (sweep)  | Other lesions FDG SUVmax  |
|----------|--|---------------------------|--|---|-------------------|-------------------------------|--|---|
| 1-013    | Ultrasound guided liver biopsy                                   | 23                        | 5  | --  | --                |                               | 0.9 (Sacrum)   | 17.3  |
| 2-016    | Lung, RLL wedge resection  | -62                       | 0  | --  | --                | --                            | 0.7 (T4)<br>1.2 (R Hilar LN)   | 3.5<br>3.0  |
| 3-001    | CT guided needle biopsy of T10 vertebral body                    | 5                         | 0  | 0.5   | 6.7               | 0.0                           | 0.8 (R paratracheal)<br>0.9 (R hilar)<br>1.0 (Subcarina)<br>0.8 (L hilar)  | 8.5<br>4.6<br>3.9<br>3.2  |
| 4-014    | Sacral bone biopsy   | 2                         | 0  | --  | 5.3               | 0.6                           | 0.7 (C7)<br>0.3 (T9)<br>0.8 (T3)<br>1.0 (L4)<br>0.4 (R Rib)<br>0.6 (R Femur)<br>0.6 (T11)  | 5.2<br>3.7<br>4.9<br>4.7<br>2.7<br>4.2<br>4.1                                     |
| 5-011    | Liver biopsy   | 15                        | --<br>(ER+ by clinical read; primary 10 months earlier was Allred 3) | --  | --                | --                            | 0.6 (R Paratracheal)<br>0.2 (T10)<br>0.9 (R Lung)<br>0.5 (L5)<br>0.8 (R Hilar)<br>0.8 (R Supraclav)<br>0.2 (T9)<br>1.0 (L Paratracheal)<br>0.7 (L Supraclav)<br>0.4 (Sacrum)<br>0.2 (T12)<br>0.3 (R Femur) | 9.4<br>7.2<br>11.2<br>7.5<br>6.5<br>6.1<br>4.2<br>7.5<br>4.3<br>5.2<br>7.1<br>3.8 |
| 6-018    | R breast core biopsy; L Iliac crest CT guided needle core biopsy | 12; -11                   | 7;<br>Met weakly ER+ by clinic read                                  | 1.8;<br>--                                    | 3.4;<br>--        | 2.0;<br>--                    | 1.4 (R Hilum)<br>1.3 (R Axilla Low)<br>1.3 (R Axilla Deep)   | 1.8<br>1.3<br>1.3   |
| 8-003    | Core biopsy - bone, L acetabulum; L                              | 20; 85                    | 6; 8   | --  | 3.7 (L iliac)     | 1.9 (L iliac)                 | 1.4 (R Post Rib)<br>2.7 (L SI)<br>1.1 (R Sacrum)   | 5.3<br>8.0<br>3.8   |

|        |  |           |   |                          |  |   |   |  |
|--------|--|-----------|---|--------------------------|--|---|---|--|
|        | breast mastectomy  |           |   |                          |  |   | 1.8 (L Spine)<br>2.2 (T spine)<br>1.3 (R Ischium)<br>1.4 (L Chestwall)<br>1.1 (L Supraclav)   | 5.4<br>5.6<br>4.2<br>3.9<br>2.9                                    |
| 9-017  | L breast core biopsy;<br>R Iliac crest lesion, CT guided FNA | 12;<br>17 | 8;<br>Met<br>ER+ by<br>clinical<br>read | 1.7;<br>--               | 2.7;<br>5.2                                      | 1.7;<br>3.4                                   | 1.1 (7th Lamina)<br>1.2 (L Post 4th Rib)<br>3.8 (L C1)<br>1.8 (8th Vertebral Body)<br>5.0 (R Pubis)<br>4.4 (L Ileum)<br>2.5 (L4)<br>1.7 (L 3rd Rib)<br>3.4 (L3)<br>2.1 (L Axilla) | 6.1<br>3.8<br>7.2<br>3.4<br>7.4<br>7.1<br>3.9<br>2.9<br>4.6<br>3.5 |
| 10-015 | R breast core biopsy   | 39        | 8                                       | 2.8                      | 4.7  | 2.4   | 0.7 (R Paratracheal LN)<br>0.5 (R Iliac)<br>1.4 (C5)  | 4.7<br>3.0<br>3.5  |
| 11-019 | L axillary core biopsy                                       | 61        | 8                                       | 1.6 (Mid)<br>2.6 (Lower) | 5.2 (Mid)<br>9.3<br>(Lower)<br>2.9<br>(Superior) | 1.2 (Mid)<br>2.0 (Lower)<br>1.1<br>(Superior) | 1.7 (R Subcarinal Node)<br>1.2 (L AP Window)<br>1.2 (R Centrl Hilar Node)<br>1.0 (R Periph Hilar Node)  | 8.9<br>3.5<br>3.6<br>2.3   |
| 12-020 | T7 Vertebrae, CT guided core biopsy                          | 28        | 8                                       | 2.8                      | 7.1  | 3.3   | 2.4 (R Humeral Head)  | 7.1<br>2.5   |
| 13-008 | R Scapula, CT guided FNA                                     | 8         | 8                                       | 2.9                      | 4.6  | 2.5   | 2.4 (L4)<br>2.9 (L ParaAortic 2)<br>2.5 (L ParaAortic 1)  | 6.1<br>6.3<br>4.5  |
| 14-006 | R supraclav LN core biopsy                                   | 7         | 8                                       | 3.9                      | 11.2   | 3.9   | 2.9 (R Mid Axilla)<br>2.5 (L Spine)<br>2.0 (R 4th Rib)<br>2.9 (R Hilar LN)<br>3.4 (R Upper Mid Axilla)  | 10.1<br>8.8<br>4.2<br>5.6<br>5.9                                   |
| 15-002 | Core biopsy - L axillary mass                                | 9         | 8                                       | 1.9                      | 2.8  | 2.6   | 2.0 (L Sacrum)<br>3.5 (R Subcarina)<br>2.0 (L Supraclav)<br>4.2 (High R Paratracheal)<br>3.3 (T8)<br>2.5 (L2)<br>2.3 (Sternum)<br>3.5 (R Hilar)                                   | 4.3<br>5.6<br>3.7<br>6.1<br>4.7<br>3.8<br>3.2<br>5.0<br>4.2        |

|        |  |    |   |                       |     |                       |  |  |
|--------|--|----|---|-----------------------|-----|-----------------------|--|--|
|        |  |    |   |                       |     |                       | 3.0 (R Paratracheal)<br>3.3 (L Hilar)  | 3.4                                    |
| 17-009 | Liver biopsy                             | 16 | 8 | --                    | --  | --                    | 3.8 (Sternum)<br>2.5 (L Humerus)<br>4.2 (RetroSternal Node)<br>2.0 (L Humeral Head)<br>4.5 (Mesenteric Mass 1)<br>4.5 (Mesenteric Mass 2)      | 6.3<br>4.5<br>6.4<br>3.4<br>5.2<br>4.0 |
| 18-004 | L chest wall and pleural effusion biopsy | 70 | 8 | (all from chest wall) |     | (all from chest wall) | 3.7 (Superior Apical)<br>5.6 (Anterior Apical)<br>4.3 (L Apical)<br>6.0 (Superior Medial)<br>4.6 (Posterior Lateral)<br>4.3 (Posterior Medial) | 3.6<br>3.9<br>2.6<br>2.6<br>2.5<br>2.4 |
| 19-005 | R breast core biopsy                     | 14 | 8 | 5.5                   | 2.5 | 5.6                   | 6.5 (Medial Node)<br>8.3 (Mediastinum)<br>5.2 (R Pleura)<br>2.5 (Inferior R Breast)<br>4.1 (R IM)  | 5.6<br>6.5<br>5.0<br>1.8<br>2.7        |

Appendix Figure: Association between quantitative FES uptake measures and ER expression, for all lesions of patients with imaging and biopsy. (Figure 3 only shows imaging results for biopsied lesions). Panel A: FES SUVmean (dynamic scan) and Allred score. Panel B: FES SUVmean (torso scan) and Allred score.

