Phase II Trial of Bicalutamide in Patients with Androgen Receptor Positive, Hormone Receptor Negative Metastatic Breast Cancer

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Running title: Bicalutamide in AR(+) ER/PgR(-) Metastatic Breast Cancer

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Translational relevance statement

Genome wide transcriptional analysis identified a subset of androgen receptor (AR) positive, ER/PR-negative breast cancers. In vitro studies confirmed the functional role of AR and demonstrated that growth could be abrogated by antiandrogens. We conducted this multicenter phase II trial of the oral AR-inhibitor bicalutamide in patients with AR(+) ER/PR(-) metastatic breast cancer to test the hypothesis that androgen blockade could benefit patients with androgen-dependent, estrogen-independent cancer. This is the first clinical trial to report activity of antiandrogen therapy in breast cancer and establishes the potential of targeting AR in ER(-) disease.
Abstract

Purpose: Patients with hormone receptor-negative breast cancer (BC) generally do not benefit from endocrine-targeted therapies. However, a subset with androgen receptor (AR) expression is predicted to respond to antiandrogen therapies. This phase II study explored bicalutamide in AR positive, estrogen receptor (ER) and progesterone receptor (PgR)-negative metastatic breast cancer.

Experimental Design: Tumors from patients with ER/PgR-negative advanced breast cancer were tested centrally for AR (Immunohistochemistry (IHC) > 10% nuclear staining considered positive). If either the primary or a metastatic site was positive patients were eligible to receive the AR-antagonist bicalutamide at a dose of 150 mg daily. Clinical benefit rate (CBR), the primary endpoint, was defined as the total number of patients who demonstrate a complete response (CR), partial response (PR) or stable disease (SD)>6 months; secondary endpoints included progression-free survival (PFS) and toxicity. Correlative studies included measurement of circulating endocrine markers and IHC surrogates for basal-like breast cancer.

Results: Of 424 patients with ER/PgR-negative breast cancer, 12% tested AR-positive. The 6-month CBR was 19% (95% CI 7-39%) for bicalutamide. The median PFS was 12 weeks (95% CI 11-22 weeks). Bicalutamide was well tolerated with no grade 4/5 treatment-related adverse events observed.

Conclusion: AR was expressed in 12% of patients with ER/PgR-negative breast cancer screened for this trial. The CBR of 19% observed with bicalutamide demonstrates proof-of-principle for the efficacy of minimally toxic androgen blockade in a select group of patients with ER/PgR negative, AR-positive breast cancer.
Introduction

Estrogen and the estrogen receptor (ER) have been well-recognized and highly effective targets for the treatment of ER (and progesterone receptor (PgR))-positive breast cancers. Yet patients with breast cancer that truly lacks expression of the estrogen and progesterone receptors have not traditionally derived benefit from conventional endocrine therapies such as selective estrogen receptor modulators or aromatase inhibitors. For those patients with triple negative breast cancer (TNBC), whose tumors also lack overexpression or amplification of HER2, standard palliative systemic treatment options are limited to cytotoxic chemotherapy agents. Patients diagnosed with advanced TNBC may respond initially to chemotherapy but the duration of response is often short and there is a higher likelihood of visceral metastases, rapidly progressive disease and inferior survival outcomes compared to the other subtypes (1-3).

A comprehensive molecular analysis of 99 archived primary breast tumors at Memorial Sloan-Kettering Cancer Center (MSKCC) previously identified a subset of ER/PgR-negative cancers that associated with ER(+) tumors and expressed a molecular profile suggestive of active hormonal signaling without expression of ER or PgR. This subset represented ~22% of ER/PgR(-) cancers and had a transcription profile that resembled molecular apocrine or luminal AR (4-7). Further evaluation confirmed the absence of ER and revealed overexpression of the androgen receptor (AR). The functional role of AR was established by the AR-dependent, estrogen-independent growth observed in response to synthetic androgen, estrogen and ER-
antagonist exposure using an MDA-MB-453 cell line representative of this subset of ER/PgR-negative breast cancer (4).

Based on the observations above, we hypothesized that AR-inhibition would have antitumor activity for patients with AR(+) ER/PgR(-) advanced breast cancer. Bicalutamide is an oral, nonsteroidal, AR-antagonist that is approved by the Food and Drug Administration for use in combination with luteinizing hormone-releasing hormone (LHRH) analogs for the treatment of metastatic prostate cancer. Data for the use of antiandrogens in women have been reported from small studies when used as treatment of hirsutism, polycystic ovarian syndrome or ovarian cancer in women with elevated ovarian androgen production at baseline. However, these data regarding the effect of antiandrogens on circulating androgens and estrogens are limited and in one case, confounded by coadministration of an LHRH agonist.(8-11)

We conducted a multicenter phase II, proof-of-concept trial testing bicalutamide for the treatment of women with AR(+) ER/PgR(-) metastatic breast cancer (MBC). We measured serial levels of free and total testosterone, estradiol and sex hormone binding globulin. Cytokeratin 5/6 and EGFR were tested to apply Nielsen criteria as a surrogate for basal-like breast cancer.(12)

Methods

Study design

This open-label, single-arm study was initially opened at MSKCC and later expanded to 7 additional centers through the Translational Breast Cancer Research Consortium (TBCRC). The
primary objective was to evaluate the efficacy of oral bicalutamide, 150 mg/day for the
treatment of women with AR+ ER/PgR-negative MBC. The primary endpoint was clinical benefit
rate (CBR), defined as the total number of patients who demonstrate a complete response (CR),
partial response (PR) or stable disease (SD)>6 months. Secondary endpoints included
progression-free survival (PFS), safety and toxicity assessments and correlative science studies.
Enrollment required 2 steps: (1) consent to determine AR status, which was permitted while on
another therapy for breast cancer, followed by (2) consent to the therapeutic portion of the
trial for patients with centrally confirmed AR(+) ER/PgR(-) MBC.

**Patient eligibility**

Four hundred fifty-two patients with histologically confirmed ER/PgR-negative
(Immunohistochemistry (IHC) ≤ 10%) MBC consented for AR testing at participating TBCRC
institutions from March 2007 through January 2012. Patients were eligible for the therapeutic
portion of the trial if they had ER/PgR-negative unresectable locally advanced or metastatic
disease and formalin-fixed paraffin-embedded tumor from either the primary or a metastatic
site tested positive for AR (IHC > 10% nuclear staining) using a commercially available antibody
(Dako, AR 441; dilution: 1:300). Initially local testing at study sites was permitted with central
confirmation at MSKCC. Nine of 43 patients who elected to have local AR testing were AR(+) locally. Four of the 9 patients were AR(-) on central testing. Given this discordance, as of
August 2010 all testing was performed centrally at MSKCC for standardization of methods.

Additional eligibility criteria included measurable or nonmeasurable disease per
Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, Eastern Cooperative
Oncology Group performance status < 2 and adequate hepatic, renal, and hematologic
function. There was no limit on prior therapies, except prior trastuzumab was required for patients with HER2-positive disease (IHC 3+ or FISH >2.0). Exclusion criteria included chemotherapy within 2 weeks and investigational therapy within 3 weeks. The institutional review boards of the participating centers approved this protocol. All patients gave written informed consent (NCT00468715).

Treatment

Bicalutamide 150 mg was administered orally on a continuous daily schedule. Patients were treated until disease progression or unacceptable adverse events. A maximum of two dose reductions for grade ≥ 3 toxicity were allowed (100 mg, 50 mg). A maximum of 2 weeks was permitted for treatment delays due to toxicity.

Patient evaluation

Patients were evaluated for toxicity at the time of each 4-week treatment cycle, according to the National Cancer Institute Common Toxicity Criteria, version 3.0 (NCI-CTC v3.0). Radiographic response was evaluated every 12 weeks with radiographic scans that were reviewed at each site by a designated study radiologist, according to RECIST.

Statistical analysis

This study was designed as a single-stage, phase II which required a total of 28 patients to discriminate between true clinical benefit rates of ≤ 5% and ≥ 20% at a type I error of 5% and a type II error of 16%. If 4 or more patients had a CR, PR or SD>6 months, bicalutamide would be considered to have activity in this patient population and would merit further clinical study. PFS was defined from start of therapy to progression of disease or last date of follow-up and analyzed using Kaplan-Meier methods. Response rates were calculated with 95% exact
confidence intervals (CIs). Toxicities were summarized using NCI-CTC v3.0, and the maximum grade per patient was used as the summary measure.

**Correlative Studies**

Peripheral blood was obtained at baseline, start of Cycle 2 (C2) and end of study (EOS) to measure total and free testosterone (T), estradiol (E) and sex hormone binding globulin (SHBG) using a commercially available assay. Summary statistics such as mean, median, and proportions were calculated for these values. Wilcoxon signed-rank test was performed to compare baseline to C2 and EOS values. Percent change for each endocrine biomarker from baseline was examined to account for variations in baseline values.

Unstained slides or tissue blocks representative of malignant AR(+), ER/PR(-) tissue were stained for CK5/6 (Dako D5/16 B4; dil 1:200) and EGFR (Invitrogen 31G7; dil 1:100) using standard immunoperoxidase techniques by the core facility at Memorial Sloan-Kettering Cancer Center. Staining intensity was reviewed and scored by the study pathologist as follows: percent cells staining and the intensity of staining (0 no staining, 1+ mild, 2+ moderate and 3+ strong intensity). Data will be presented in tabular form and analysis is primarily exploratory and hypothesis generating.

**Results**

**Patient demographics**

Twelve percent (51/424) of screened patients tested AR(+). Fewer than 10 of the patients who tested negative for AR expression had staining in the range from 1-10% by IHC. Thirty-two of the 424 patient samples tested were HER2-positive (7.5%) and 7 were positive for
both AR and HER2. Of the 452 patients consented for testing, 28 did not undergo testing as they had either insufficient tissue (n=17), tested ER(+) (4), died before testing (2), withdrew consent (3), consented after the close of trial (1), or did not have confirmed metastatic disease (1). Eight patients whose tumors tested AR+ were ineligible for treatment due to testing ER(+) centrally (2), developing a second primary cancer (1), not meeting all of the prespecified eligibility criteria (2), or having a significant decline in performance status (3). Fifteen patients were eligible for bicalutamide but continued on effective treatment and thus were not enrolled on the therapeutic portion of the trial before it reached its accrual goal. Twenty-eight patients were treated on study (Fig. 1). Two patients who initiated bicalutamide were later found to be ER(+) and were removed from study—one at the time of PD and the other at the time of central confirmation. Patient characteristics are shown in Table 1. Study participants had a median age of 66 years (range 41-83) and ECOG performance status (median 0, range 0-1). The majority had visceral metastases and received a median of 1 (0-8) prior line of chemotherapy for metastatic disease.

Efficacy

Twenty-six study participants with AR(+) ER/PgR(-) MBC were evaluable for the primary endpoint. Five patients had stable disease >6 months (number of cycles completed: 6, 8, 10+, 13, 57+) as their best response on treatment. There were no confirmed complete or partial responses yielding a clinical benefit rate of 19% (95% CI 7-39%) in the target population (n=26). In an intention to treat analysis, a CBR of 18% (95% CI 6-37%) was observed. One patient with unresectable, locally advanced, ER/PgR/HER2-negative breast cancer following neoadjuvant anthracycline- and taxane-based therapy had stable disease per RECIST after 6 months on study.
but was then able to undergo curative breast surgery. At the time of mastectomy, she was found to have HER2(+) cancer and subsequently received 1 year of trastuzumab.

Clinicopathologic features of the 5 patients deriving clinical benefit from therapy are shown in Table 2. Two patients had stable disease <6 months, and 19 patients had disease progression as best response. We delivered a median of 3 cycles of therapy (2-57+) and 2 patients remain on treatment after 57+ and 11+ cycles. Median PFS was 12 weeks (95% CI 11-22 weeks) (Fig. 2).

**Adverse events**

The most common, possibly drug-related toxicities of any grade were fatigue (6/28), hot flashes (6/28), limb edema (6/28), AST elevation (7/28) and ALT elevation (6/28). Grade 1 toxicities reported in >10% of patients on study are shown in Table 3. There were few grade 2 or 3 adverse events associated with bicalutamide (Table 3). All grade 3 liver enzyme abnormalities (elevation in AST, bilirubin, and alkaline phosphatase) were documented in 1 patient with known liver metastases who had progressed on therapy. Thus it remains unclear whether these laboratory findings were attributable to bicalutamide therapy or disease progression. There were no grade 4 or 5 events or treatment-related serious adverse events. Two patients had dose delays as a result of grade 2 AST elevations later determined to be related to disease progression in the liver. One patient had a protocol-stipulated dose reduction to 100 mg for cerebrovascular ischemia that was later determined to be related to poorly controlled hypertension rather than study drug; she remains on therapy with stable disease.

**Correlative Endpoints**

*Serum hormone levels:*
Ninety two percent of evaluable patients at baseline were postmenopausal. Evaluable patients numbered 26, 26 and 19 at baseline, C2 and EOS respectively. Median free and total T, estradiol and SHBG are shown in Supplemental Fig. 1 as boxplots. No discernible patterns of change in serum hormone levels were observed in response to bicalutamide therapy. There was no difference in median percent change observed across time points for each endocrine biomarker examined (Supplemental Table 1/Figure 2).

Immunohistochemical characterization of basal-like breast cancer:

Four patients (15%) had sufficient invasive tumor adequate for correlative IHC following testing of ER, PR and AR. The results of CK 5/6, EGFR, HER2 and ER staining are shown in Table 4. One of the 4 patients had clinical benefit to bicalutamide and lacked expression of basal-like cytokeratins and EGFR. Two non-responders demonstrated expression of both CK 5/6 and EGFR, suggestive of a basal-like subtype rather than an AR-dependent one.

Discussion

Based on the results of the screening stage of this trial, AR is expressed in 12% of patients with ER/PgR-negative breast cancer. Our patient population largely represented TNBC, with the majority of patients having HER2-normal cancers. In this selected subset of patients with AR(+) ER/PgR(-) metastatic breast cancer, this study met its prespecified endpoint, demonstrating a clinical benefit rate of 19% for bicalutamide 150 mg by mouth daily. This therapy was well tolerated with the most common treatment-related adverse events including fatigue, hot flashes, limb edema, and transaminase elevations.
This is the first clinical trial to report activity of anti-androgen therapy in advanced breast cancer and establishes the potential of targeting AR in AR-dependent, ER-independent disease. Previous studies that examined the use of flutamide, an oral antiandrogen, for the treatment of metastatic breast cancer concluded a lack of meaningful antitumor activity. However these small phase II trials were conducted in unselected patient populations irrespective of AR, ER or PgR (13, 14).

Overall, AR is expressed in about 77% of breast cancers and co-expression with ER is common (15-17). In contrast, the literature suggests expression of AR in ~20-50% of ER-negative breast cancers (4, 15). This wide range may be attributed to the retrospective nature of these studies and the biases inherent to this type of analysis, variability in patient selection from archival specimens (i.e., primary tumors vs. metastases; co-expression of HER2), differing assays for AR testing or other factors not yet realized. Our prospective screening experience in this study of more than 450 patients with ER/PgR(-) cancers found that about 12% expressed nuclear staining of AR in excess of 10%. The immunohistochemical methods on study utilized the same commercially available antibody from the preclinical studies that informed the design of our trial. Although the observed AR rate of 12% is lower than that previously reported, it is consistent with more recent reports from a triple negative breast cancer dataset in which 10% of over 170 breast cancer primary tumors tested AR(+).(18)

We observed clinical features in this population of patients with AR(+) ER/PgR(-) breast cancers that differ from those that typically characterize TNBC. The median age of 66 years was higher than the mean age at diagnosis for patients with TNBC, which is usually more than a decade earlier (approximately 53 years of age) (3). Sites of metastases in our study often
included nodal, soft tissue and bone, whereas triple negative breast cancers have been noted to have patterns of spread preferentially to brain, lungs and other viscera (19-21).

While correlative science studies are ongoing to investigate potential genomic predictors of response to antiandrogen therapy, we observed that those patients who derived clinical benefit from bicalutamide received treatment in the first or second-line setting. All patients had substantial AR expression, measuring 20% to >90%. One patient who had prolonged stable disease for >12 months had weak ER expression measuring 3%. At the time of study accrual, ASCO/CAP guidelines had not yet lowered the threshold defining ER-positivity to its current level of 1% or greater (22). We elected to maintain eligibility criteria as previously specified due to the recognized heterogeneity within TNBC. Preclinical cell-line models from Doane et al demonstrated estrogen-independence in this molecular subtype; therefore, the impact of weak ER expression for this 1 patient is unclear. In addition, recent preclinical data demonstrated that bicalutamide did not inhibit estrogen-mediated proliferation of ER+ breast cancer cells.(23)

Recent reports suggest that triple negative breast cancers may be divided into as many as 6 subtypes based on molecular profiling, 1 of which is defined as luminal AR and marked by hormone-regulated pathways with expression of higher levels of AR mRNA than the other subtypes (6). We hypothesized that the absence of basal-like breast cancer IHC markers would predict for response to antiandrogen therapy as this AR-dependent subtype of breast cancer is distinct from the basal-like subtypes (BL1 and BL2) described by Lehmann et al (6). Our findings are consistent with this hypothesis, albeit limited by the small numbers available for analysis. One patient with prolonged stable disease lacked expression of CK 5/6, EGFR and HER2
whereas two-thirds of the non-responders expressed the Nielsen criteria suggestive of the basal-like subtype.

One of the patients with response to therapy had unresectable locally advanced ER/PgR(-), HER2 1-2+/FISH 1.1 breast cancer following neoadjuvant anthracycline and taxane-based therapy. After 6 months of study treatment, she had tumor reduction sufficient to enable definitive breast surgery but did not meet RECIST for partial response. At the time of mastectomy, she was found to have HER2 overexpression (IHC 3+) and went on to receive 1 year of adjuvant trastuzumab off-study. Interestingly, AR expression has been reported in ~50-60% of HER2-positive breast cancers (15, 24-26), and others have found a significant number of ER(-)/HER2(+) breast tumors that express AR and exhibit androgen-dependent growth. It has also been shown that androgen stimulates tumor cell growth through Wnt and HER2 signaling pathways via AR-dependent upregulation of WNT7B and HER3 (27). Functionally significant cross-talk between AR- and HER2-signaling pathways in ER(-) breast cancer has also been demonstrated in molecular apocrine cell lines by inhibition of heregulin-mediated growth with the use of flutamide. Synergy with combined use of flutamide and the anti-ErbB2 AG825 has been shown with respect to cell proliferation and apoptosis, suggesting a potential clinical advantage to combination therapy for AR(+), ER(-), HER2(+) breast cancers (28).

Median PFS in this study was 12 weeks, a rate comparable to that reported for single-agent or combination chemotherapy in multiple recent trials conducted in the triple negative population (29-31). The disease stabilization observed in 5 patients on this study is encouraging, and suggests a signal of activity for androgen blockade in AR (+) ER/PgR (-) breast cancer. However, given the generally aggressive clinical course associated with TNBC, these findings
may alternatively reflect identification of a more indolent subtype of the disease characterized by AR expression. This possibility is supported by the observation that the clinical characteristics of this cohort appeared to differ from the traditional TNBC clinical features as described above. This remains an area of investigation to be answered by future trial designs.

This study highlights the challenges of drug development in the era of “precision medicine.” Targets may be rare, responses may not meet criteria per RECIST, and individual centers may not be able to complete such studies. At the same time, this study is proof-of-concept for the utility of targeting AR when positive in patients with ER/PgR(-) breast cancers. Although this subgroup represents a small percentage of all breast cancers (15% of breast cancers are triple negative, 12% of these are AR+, meaning that only 2% of all patients have tumors in this subset), the absolute numbers are nonetheless clinically meaningful. Two percent of the over 200,000 women diagnosed with breast cancer in the United States in 2012 yields 4,000 potential patients (32). For the subset of these who develop metastatic disease, the opportunity to receive minimally toxic, oral, endocrine therapy with clinical benefit is a new treatment option.

There are additional challenges to the development of AR targeting agents in women with metastatic breast cancer. As in other settings, there are no validated biomarkers of response to anti-androgen therapy. To that point, our exploration of serum hormone levels did not appear to offer utility as a pharmacodynamic marker of bicalutamide activity.(33) The full potential of targeting AR in both ER(-) and ER(+) breast cancers is not yet explored and the possibility of dual pathway inhibition of androgen and HER2, MEK or PI3K/AKT as suggested by preclinical trials is unexplored clinically (6, 27, 28, 34, 35). Perhaps equally challenging will be
the feasibility of drug development through conventional randomized phase III trials for the small population of patients expressing this target. To this end, trials are ongoing to test the safety and feasibility of next-generation, novel androgen-targeted therapies such as enzalutamide (NCT01597193) in this patient population, but new regulatory approaches to establishing their efficacy may be needed.

Grant Support

This trial was supported in part by the Translational Breast Cancer Research Consortium, Breast Cancer Alliance, and AstraZeneca.
References


Figure Legend

Table 1. Characteristics of patients with AR(+) tumors

(Caption) aHER2-positive defined as IHC 3+ or fluorescence in situ hybridization >2.
†TBCRC011 involved a two-step enrollment process which allowed patients with ER/PgR(-) breast cancer that was metastatic to be tested for AR without enrolling in the therapeutic portion of the trial. Therefore, the patients who tested AR-positive but did not consent to therapy did not have clinical data collected aside from ER, PR, HER2, age and site of disease tested for AR.

Table 2. Characteristics of patients with clinical benefit
(Caption) Abbreviations: DOR, duration of response; NA, not applicable; NR, no response; LABC, locally advanced breast cancer

Table 3. Bicalutamide-related adverse events per NCI CTCAE version 3
(Caption) aGrade 1 toxicities reported in >10% of patients (n=28). No grade 4 or 5 events or treatment-related serious adverse events observed.

Table 4. Use of Nielsen Criteria as a surrogate for basal-like breast cancer. Absence of basal-like markers may correlate with response to anti-androgen therapy.

Figure 1. CONSORT diagram

Figure 2. Progression-free survival (PFS) on oral daily bicalutamide 150 mg
Table 1.

<table>
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<td>No. of pts (n)</td>
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<td>66 (41-83)</td>
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<td>Median ECOG PS (range)</td>
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<td>0 (0-1)</td>
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<td>Median number of regimens (range)</td>
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Table 2.

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<th>PgR%</th>
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Table 3.

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<tr>
<td>Alkaline Phosphatase</td>
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</tr>
<tr>
<td>Nausea</td>
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<td></td>
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</tr>
<tr>
<td>Pain</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Headache, back, other</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>3</td>
<td></td>
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<tr>
<td>Limb</td>
<td>3</td>
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<tr>
<td>Constipation</td>
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<tr>
<td>Anorexia</td>
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<td>Fatigue</td>
<td>5</td>
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<td>Hemoglobin</td>
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<tr>
<td>Vaginal Dryness</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Hot flashes</td>
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<tr>
<td>Limb edema</td>
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Table 4.

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<th>ER</th>
<th>HER2</th>
<th>CK5/6</th>
<th>EGFR</th>
<th>Best Response</th>
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</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>0%</td>
<td>1+</td>
<td>0%</td>
<td>0%</td>
<td>POD &lt; 3MO</td>
</tr>
<tr>
<td>Patient 2</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>0%</td>
<td>SD &gt; 6MO</td>
</tr>
<tr>
<td>Patient 3</td>
<td>0%</td>
<td>0</td>
<td>10%</td>
<td>10%</td>
<td>POD 3MO</td>
</tr>
<tr>
<td>Patient 4</td>
<td>0%</td>
<td>0</td>
<td>25%</td>
<td>&lt;10%</td>
<td>POD 3MO</td>
</tr>
</tbody>
</table>
Figure 1.

- **Consented for AR testing (n=452)**
  - **Screened for AR expression (n=424)**
    - **AR(+) (n=51)**
      - **On study (n=28)**
    - **AR(-) (n=373)**
      - **Ineligible for therapy (n=8)**
      - **Eligible for therapy; trial closed to accrual (n=15)**
      - **Ineligible post therapy (n=2)**
  - **Ineligible for testing (n=28)**
    - **Eligible on study (n=26)**

**Research.**
Figure 2.

# at risk: 26

Weeks from Treatment Start

0 12 24 36 48 60 72 84 96 108 120

N = 26 (PFS events = 23)

Median PFS: 12 weeks, 95% CI: (11, 22)
Clinical Cancer Research

Phase II Trial of Bicalutamide in Patients with Androgen Receptor Positive, Hormone Receptor Negative Metastatic Breast Cancer

Ayca Gucalp, Sara Tolaney, Steven J. Isakoff, et al.

Clin Cancer Res  Published OnlineFirst August 21, 2013.

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Supplementary Material  Access the most recent supplemental material at: http://clincancerres.aacrjournals.org/content/suppl/2013/08/21/1078-0432.CCR-12-3327.DC1

Author Manuscript  Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

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