Clinical and Translational Results of a Phase II, Randomized Trial of an Anti–IGF-1R (Cixutumumab) in Women with Breast Cancer That Progressed on Endocrine Therapy

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Abstract

Purpose: This phase II trial evaluated the efficacy and safety of cixutumumab, a human anti–insulin-like growth factor receptor 1 (IGF-1R) monoclonal IgG1 antibody, and explored potential biomarkers in postmenopausal women with hormone receptor–positive breast cancer.

Experimental Design: Patients with hormone receptor–positive breast cancer that progressed on antiestrogen therapy received (2:1 randomization) cixutumumab 10 mg/kg and the same antiestrogen (arm A) or cixutumumab alone (arm B) every 2 weeks (q2w). Primary endpoint was progression-free survival (PFS); secondary endpoints included overall survival (OS) and safety. Correlative analyses of IGF-1R, total insulin receptor (IR), and IR isoforms A (IR-A) and B (IR-B) expression in tumor tissue were explored.

Results: Ninety-three patients were randomized (arm A, n = 62; arm B, n = 31). Median PFS was 2.0 and 3.1 months for arm A and arm B, respectively. Secondary efficacy measures were similar between the arms. Overall, cixutumumab was well tolerated. IGF-1R expression was not associated with clinical outcomes. Regardless of the treatment, lower IR-A, IR-B, and total IR mRNA expression in tumor tissue was significantly associated with longer PFS [IR-A: HR, 2.62 (P = 0.0062); IR-B: HR, 2.21 (P = 0.0202); and total IR: HR, 2.18 (P = 0.0230)] and OS [IR-A: HR, 2.94 (P = 0.0156); IR-B: HR, 2.69 (P = 0.0245); and total IR: HR, 2.72 (P = 0.0231)].

Conclusions: Cixutumumab (10 mg/kg) with or without antiestrogen q2w had an acceptable safety profile, but no significant clinical efficacy. Patients with low total IR, IR-A, and IR-B mRNA expression levels had significantly longer PFS and OS, independent of the treatment. The prognostic or predictive value of IR as a biomarker for IGF-1R–targeted therapies requires further validation.

Introduction

Approximately 70% to 75% of breast cancers are positive for expression of the estrogen receptor (ER; ref. 1). For patients with hormone receptor–positive tumors, the preferred first-line treatment comprises blockade of estradiol synthesis or hormone receptor activity using aromatase inhibitors or antiestrogen agents. Although endocrine therapies are useful and well tolerated, most patients with metastatic breast cancer respond to this form of treatment for approximately 12 to 18 months before developing refractory disease (2). Resistance to sequential hormonal therapies can potentially lead to tumors with complete hormone independence (2, 3). New therapeutic modalities able to provide additional benefit to patients with hormone receptor–positive, antiestrogen refractory, advanced and metastatic breast cancer are required.

A growing body of evidence has implicated the overexpression of insulin-like growth factor receptor 1 (IGF-1R) in the development of resistance to antiestrogen therapy in hormone receptor–positive breast cancer (4, 5). Santen and colleagues investigated the mechanism by which breast cancer tumor cells develop resistance to antiestrogen therapy and posited that tumors adapt despite antiestrogen treatment, developing enhanced sensitivity...
Translational Relevance
This randomized, open-label, phase II trial evaluated the efficacy and safety of cixutumumab in patients with hormone receptor–positive, advanced or metastatic breast cancer refractory to antiestrogen therapy (NCT00728949). In addition, this study aimed to address the critical unmet need for the development of biomarkers for insulin-like growth factor receptor 1 (IGF-1R)–targeted therapies. In particular, mRNA expression of insulin receptor (IR)-A, IR-B, and total IR in tumor tissue was significantly associated with progression-free survival and overall survival in this study (lower marker levels corresponded with better outcomes). These results indicate that any potential practical use of IR as a predictive or prognostic biomarker would require clinical validation prior to use in guiding patient treatment.

to the growth-promoting effects of estradiol (2). Estradiol activates many signaling molecules, including IGF-1R, and it appears that estradiol hypersensitivity may be derived from interactions between estradiol and IGF-1R (3, 6). Results from a recent study suggest that targeting IGF-1R or downstream signaling components may resensitize breast cancer cells to antiestrogen therapies (7). The IGF-1R ligands IGF-I and IGF-II also mediate strong mitogenic and anti-apoptotic effects through IGF-1R in several cancer cell lines, including breast cancer (8). Additionally, the use of IGF-1R inhibitors has profound effects on the growth of tamoxifen-resistant breast cancer cell lines (9, 10). For example, the IGF-1R tyrosine kinase inhibitor AG1024 reduced the proliferation of tamoxifen-resistant cells in a dose-dependent manner as well as the phosphorylation of IGF-1R and known downstream signaling molecules (9). The monoclonal antibody mAb3 inhibits the growth of tamoxifen-resistant cancer cells by 50% when compared with tamoxifen-sensitive cells (10). Taken together, the data suggest that blocking the binding of growth factors upstream of these pathways to their receptors might prevent this adaptive estradiol hypersensitivity and thus ameliorate antiestrogen resistance (2).

The insulin receptor (IR), which is closely related to IGF-1R, is also overexpressed in breast cancer cells. Studies with insulin analogues, blocking and stimulating anti-IR antibodies, small molecule inhibitors, and various strains of mice have demonstrated a role for IR in breast cancer development and progression (11–13). IR is found as two isoforms, IR-A and IR-B, as a result of alternative splicing (14, 15). Harrington and colleagues demonstrated that IR-A is more predominant than IR-B in breast cancer (16). Insulin binds to both isoforms with comparable affinity; however, IGF-II, which is expressed by breast cancer tumor stroma, binds with high affinity to IR-A but not IR-B (12, 15). Tissue-specific expression and differential ligand-binding specificity indicate a functional significance for these two isoforms (15). Although their individual roles have not been completely elucidated, IR-B is more associated with metabolic signaling, whereas IR-A is more associated with mitogenic signaling and anti-apoptotic effects (17). IGF-II activates IR-A to initiate proliferative, prosurvival, and metabolic signaling, which may limit the antitumor activity of antibodies that only block the interaction of IGF-II with IGF-1R (16–19). These data implicate IR-A as a possible predictive biomarker to select and monitor patients eligible for IGF-1R-targeted therapy (16). In breast cancer, IHC studies measuring total IR protein expression have suggested a correlation between elevated IR expression and positive outcomes in primary and node-negative cancers and poor outcomes in advanced cancers (20–22).

Cixutumumab (IMC-A12, NSC742460) is a fully human anti-IGF-1R monoclonal IgG1 antibody that inhibits IGF-I and IGF-II binding and downstream signaling mechanisms (8). Data from nonclinical studies and preliminary pharmacokinetic data from phase 1 trials CP13-0501 (clinicaltrials.gov identifier NCT00785538) and CP13-0502 (clinicaltrials.gov identifier NCT00785941) suggest that cixutumumab should induce therapeutic benefit when dosed at 10 mg/kg every 14 days (8, 23). In this phase II trial (ClinicalTrials.gov: NCT00728949), we assessed the efficacy and tolerability of cixutumumab as a single agent to test whether hormone receptor–positive breast cancer cells that developed resistance to antiestrogen therapy may benefit from IGF-1R blockade. To understand whether IGF-1R inhibition restores tumor sensitivity to antiestrogen therapy in these patients, this study also evaluated the antitumor effect of cixutumumab in combination with antiestrogens. Given that IGF-II can activate both IGF-1R and IR-A, we hypothesized that IGF-II–mediated IR signaling may facilitate de novo resistance to IGF-1R antibodies. As a result, patients with high IR expression in tumor tissue would be unlikely to benefit from IGF-1R blockade. Therefore, the relationship between IGF-1R, IR-A, and IR-B mRNA expression in tumor tissue and clinical efficacy of cixutumumab in patients with breast cancer was also explored.

Patients and Methods
Eligibility criteria
Postmenopausal women with hormone receptor–positive (either ERs, progesterone receptors, or both) breast cancer were enrolled. Key inclusion criteria were as follows: patients age ≥18 years with an intact uterus and amenorrhea for ≥12 months who had received prior antiestrogen therapy with at least one antiestrogen agent administered for ≥3 months in the adjuvant or metastatic setting and experienced disease progression while on or within 12 months after receiving the last dose of endocrine therapy. Histologically or cytologically confirmed invasive breast cancer, which at the time of study entry was either stage III (locally advanced) disease not amenable to curative therapy or stage IV disease, and either measurable or evaluable disease were required. Patients had a life expectancy of ≥3 months and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2. Patients must have completed any prior chemotherapy and/or radiotherapy prior to the administration of the first dose of study therapy.

Key exclusion criteria included the following: the presence of uncontrolled brain or leptomeningeal metastases, the presence of poorly controlled diabetes mellitus, and prior history of allergic reactions attributed to compounds of chemical or biologic composition similar to that of cixutumumab. Patients with a history of diabetes mellitus were allowed to participate, provided that their blood glucose was within normal range (fasting glucose at study entry <120 mg/dL or below upper limit of normal) and that they were on a stable dietary and/or therapeutic regimen for this condition.
The trial was conducted according to good clinical practice guidelines, Declaration of Helsinki, and all patients gave informed consent before undergoing any study procedures.

**Study design and treatment**

This was a multicenter, open-label, randomized, phase II trial that enrolled postmenopausal patients with advanced or metastatic breast adenocarcinoma that progressed on prior antiestrogen therapy. Patients were randomized 2:1 to arms A and B, respectively. Patients in arm A and arm B received cixutumumab administered at 10 mg/kg intravenously over 1 hour every 2 weeks; however, patients in arm A also received the same dose and schedule of antiestrogen therapy to which their disease became refractory. A treatment cycle was defined as 4 weeks. Patients continued to receive treatment until there was evidence of progressive disease, unacceptable toxicity, or consent was withdrawn.

**Baseline and treatment assessments**

Patients were evaluated for response according to the Response Evaluation Criteria in Solid Tumors guidelines v.1.0 (24), with radiologic evaluation every two cycles (i.e., every 8 weeks) as is typically done in early (exploratory) phase II studies. The same imaging-based assessments were used to characterize each identified and reported lesion at baseline and at reassessment during treatment. Imaging-based evaluations (including contrast-enhanced CT scan or MRI) were preferred to evaluation by clinical examination when both methods were used to assess the antitumor effect of the treatment. The baseline tumor burden (unidimensionally measurable and nonmeasurable disease) was assessed ≥28 days prior to randomization. The investigator prospectively identified the target lesions to be followed to evaluate the patient's objective response to the therapy. Confirmatory scans were required no fewer than 4 weeks after initial documentation of objective response.

Adverse events (AEs) were summarized from the Medical Dictionary for Regulatory Activities System Organ Class and preferred term, classified from verbatim terms, and assessed at least every 2 weeks throughout the study. The incidence and percentage of patients with at least one occurrence of a preferred term were included, according to the most severe grade listed in the NCI-Common Terminology Criteria for AE (NCI-CTCAE) version 3.0 (25). Causality (relationship to study drug) was summarized separately. Laboratory results were classified according to the NCI-CTCAE, version 3.0. The incidence of laboratory abnormalities was summarized; laboratory results not corresponding to an NCI-CTCAE version 3.0 term were not graded.

**qPCR assays for IR-A, IR-B, and IGF-1R**

Pretreatment formalin-fixed paraffin-embedded tumor tissue was collected and analyzed using the qPCR assays designed, validated, and tested previously by Harrington and colleagues (16). A >50% tumor cellularity was required from the biopsied samples for qPCR analysis; no other pathology assessments were completed.

**Statistical methods**

The analyses of efficacy variables were performed on the intent-to-treat (ITT) population. All patients receiving at least one dose of study drug were included in the safety analysis. Each study arm was compared with historical standards obtained with fulvestrant (26). A median progression-free survival (PFS) of ≥4.4 months observed in either arm would warrant further investigation. Comparison between arms was performed by log-rank tests and HR determined by a Cox proportional hazards model; however, the study was not powered for the analysis of PFS.

Kaplan–Meier method was used to evaluate PFS and overall survival (OS; ref. 27). Median PFS and OS and 95% confidence interval (CI) of the medians were provided. Objective response rate [complete response (CR) + partial response (PR)] and disease control rate [DCR; CR + PR + stable disease (SD)] were presented along with the 95% CI.

In exploratory analyses, the Cox proportional hazard model was used to examine associations between each marker...
Table 1. Baseline patient demographics and disease characteristics (ITT population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Arm A (N = 62)</th>
<th>Arm B (N = 31)</th>
<th>Total (N = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>62 (100.0)</td>
<td>31 (100.0)</td>
<td>93 (100.0)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>55 (88.7)</td>
<td>26 (83.9)</td>
<td>81 (87.3)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>5 (8.1)</td>
<td>4 (12.9)</td>
<td>9 (9.7)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (3.2)</td>
<td>1 (3.2)</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>1 (1.6)</td>
<td>1 (3.2)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Not Hispanic nor Latino</td>
<td>61 (98.4)</td>
<td>30 (96.8)</td>
<td>91 (97.8)</td>
</tr>
<tr>
<td>Age, y</td>
<td>59.4 (11.1)</td>
<td>57.9 (11.2)</td>
<td>58.9 (11.1)</td>
</tr>
<tr>
<td>Median</td>
<td>61.0</td>
<td>57.6</td>
<td>59.7</td>
</tr>
<tr>
<td>Min-max</td>
<td>31.8–80.2</td>
<td>38.5–83.8</td>
<td>31.8–83.8</td>
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<td>ECOG PS, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>30 (48.4)</td>
<td>16 (51.6)</td>
<td>46 (49.5)</td>
</tr>
<tr>
<td>1</td>
<td>26 (41.9)</td>
<td>14 (45.2)</td>
<td>40 (43.0)</td>
</tr>
<tr>
<td>2</td>
<td>6 (9.7)</td>
<td>2 (6.4)</td>
<td>8 (8.6)</td>
</tr>
<tr>
<td>Prior therapy, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>47 (75.8)</td>
<td>22 (71.0)</td>
<td>69 (74.2)</td>
</tr>
<tr>
<td>Hormone</td>
<td>62 (100.0)</td>
<td>31 (100.0)</td>
<td>93 (100.0)</td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>20 (32.3)</td>
<td>13 (41.9)</td>
<td>33 (35.5)</td>
</tr>
<tr>
<td>Exemestane</td>
<td>17 (27.4)</td>
<td>8 (25.8)</td>
<td>25 (26.9)</td>
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<tr>
<td>Letrozole</td>
<td>9 (14.5)</td>
<td>5 (16.1)</td>
<td>14 (15.1)</td>
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<td>Anastrozole</td>
<td>8 (12.9)</td>
<td>6 (19.4)</td>
<td>14 (15.1)</td>
</tr>
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<td>Tamoxifen</td>
<td>5 (8.1)</td>
<td>1 (3.2)</td>
<td>6 (6.5)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (8.1)</td>
<td>0 (0.0)</td>
<td>5 (5.4)</td>
</tr>
<tr>
<td>Luteinol</td>
<td>4 (6.5)</td>
<td>1 (3.2)</td>
<td>5 (5.4)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>27 (43.5)</td>
<td>16 (51.6)</td>
<td>43 (46.2)</td>
</tr>
<tr>
<td>Pleural</td>
<td>11 (17.7)</td>
<td>5 (16.1)</td>
<td>16 (17.2)</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>3 (4.8)</td>
<td>0 (0.0)</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>7 (11.3)</td>
<td>5 (16.1)</td>
<td>12 (12.9)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (12.9)</td>
<td>2 (6.4)</td>
<td>10 (10.8)</td>
</tr>
</tbody>
</table>

Abbreviations: Arm A, cixutumumab + antiestrogen; Arm B, cixutumumab; ECOG PS, Eastern Cooperative Oncology Group performance status; ER+/−, estrogen receptor positive/negative; Min, minimum; Max, maximum; N, number of patients for each treatment; n, number of patients per category for each treatment; PgR+/−, progesterone receptor positive/negative.

aTwo patients in arm A and 3 patients in arm B received more than one prior antiestrogen therapy.

bTwenty-four patients had bevacizumab (19 in arm A, 5 in arm B), 3 patients had trastuzumab (2 in arm A, 1 in arm B), and 1 patient in arm A had tipifarnib.

(dichotomized using the cutoff points at the 25th, median, and 75th percentile of the marker distribution) and PFS and OS. Because of the small sample size in arm B, Cox regressions (28) were performed for the pooled group (arms A and B combined) and for arm A separately. P values in the respective analyses were obtained using the log-rank test (29) stratified for the marker expression class. All tests of significance were conducted at a two-sided α-level of 0.05. No multiplicity adjustments across markers and endpoints were performed.

Results

Patients and treatment

A total of 93 patients were randomized at 9 centers (Fig. 1). The efficacy analysis of the ITT population comprised 62 patients randomized to receive cixutumumab plus antiestrogen (arm A) and 31 patients randomized to receive cixutumumab monotherapy (arm B). Fourteen patients randomized to the combination arm only received cixutumumab monotherapy, and 8 patients randomized to the cixutumumab monotherapy arm received cixutumumab plus antiestrogen therapy. Thus, an exploratory analysis of efficacy was also done on the per-protocol population, comprised of 48 patients in arm A and 23 patients in arm B. Analysis of the safety population was based on actual treatment and included 56 patients who received cixutumumab plus antiestrogen (arm A) and 37 patients who received cixutumumab monotherapy (arm B). Baseline patient demographics and disease characteristics are outlined in Table 1. Covariates were generally balanced between treatment arms. Median age was slightly higher in arm A (61.0 years; range, 31.8–80.2) than in arm B (57.6 years; range, 38.5–83.8). Arm A also had more patients with an ECOG PS 2 and previous biologic therapy. Median duration of treatment with cixutumumab was 8.3 weeks (range, 2.0–160.3) in arm A, and 8.3 weeks (range, 2.0–68.9) in arm B. Median number of cycles was 2 (range, 1–40) in arm A and 2 (range, 1–17) in arm B.

Efficacy

The study did not meet the primary endpoint of PFS (Table 2, Fig. 2A). In the ITT population, the median PFS was 2.0 (90% CI, 1.9–3.4) and 3.1 (90% CI, 1.9–4.2) months for arm A and arm B, respectively. PFS rate at 6 months was 20.1% (arm A) and 15.2% (arm B). The censoring rate was 24.2% and 16.1% in臂 A and B, respectively.
arm A and arm B, respectively. Only 1 patient in arm A had a PR (1.6%), for an objective response rate of 1.6% for arm A and 0% for arm B (Table 2). Clinical benefit was assessed by DCR, which was 40.3% (95% CI, 28.1–53.6) for arm A and 51.6% (95% CI, 33.1–69.8) for arm B (Table 2).

There were 20/56 (35.7%) and 14/37 (37.8%) deaths observed for arms A and B, respectively. The median OS was 20.3 months for arm A, whereas the median OS was not reached for arm B. In arms A and B, respectively, OS rates at 12 months were 60.8% and 80.4% and at 24 months were 46.6% and 62.5% (Table 2 and Fig. 2B). In an exploratory analysis, efficacy results were not different in the per-protocol population (Supplementary Table S1).

### Safety

AEs reported in >20% of patients in either arm were weight decreased (42.9% in arm A vs. 48.6% in arm B), fatigue (39.3% vs. 54.1%), nausea (32.1% vs. 35.1%), diarrhea (23.2% vs. 40.5%), vomiting (17.9% vs. 27.0%), anorexia (16.1% vs. 27.0%), and hyperglycemia (14.3% vs. 21.6%; Table 3). Patients with any-grade AEs, any-grade or grade ≥3 study drug-related AEs, and any-grade or grade ≥3 serious AEs were similar between the treatment arms (Table 3). Grade ≥3 AEs were experienced by 22/56 (39.3%) patients in arm A and 19/37 (51.4%) patients in arm B (Table 3). The frequency of drug-related serious AEs was 5/56 (8.9%) in arm A and 2/37 (5.4%) in arm B.

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**Figure 2.** Kaplan-Meier curves of PFS and OS from the ITT population. PFS (A) and OS (B) are shown for the ITT population in arm A (solid line) and arm B (dotted line). n, number of patients; NR, not reached.
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Table 3. Adverse events reported in ≥10% (any grade, either arm) patients (safety population)

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Arm A (N = 56) n (%)</th>
<th>Number of patients</th>
<th>Arm B (N = 37) n (%)</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any TEAE</td>
<td>Any grade</td>
<td>Grade ≥3</td>
<td>Any grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td></td>
<td>55 (98.2)</td>
<td>22 (39.3)</td>
<td>36 (97.3)</td>
<td>19 (51.4)</td>
</tr>
<tr>
<td>Study drug-related AE</td>
<td>48 (85.7)</td>
<td>10 (17.9)</td>
<td>31 (83.8)</td>
<td>7 (18.9)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>16 (28.6)</td>
<td>13 (23.2)</td>
<td>11 (29.7)</td>
<td>10 (27.0)</td>
</tr>
<tr>
<td>AE leading to discontinuation of any study drug</td>
<td>6 (10.7)</td>
<td>4 (7.1)</td>
<td>2 (5.4)</td>
<td>2 (5.4)</td>
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<tr>
<td>Weight decreased</td>
<td>24 (42.9)</td>
<td>0</td>
<td>18 (48.6)</td>
<td>1 (2.7)</td>
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<td>Fatigue</td>
<td>22 (39.3)</td>
<td>2 (3.6)</td>
<td>20 (54.1)</td>
<td>3 (8.1)</td>
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<tr>
<td>Nausea</td>
<td>18 (32.1)</td>
<td>2 (3.6)</td>
<td>13 (35.1)</td>
<td>3 (8.1)</td>
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<tr>
<td>Diarrhea</td>
<td>13 (23.2)</td>
<td>0</td>
<td>15 (40.5)</td>
<td>3 (8.1)</td>
</tr>
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<td>Back pain</td>
<td>11 (19.6)</td>
<td>2 (3.6)</td>
<td>6 (16.2)</td>
<td>1 (2.7)</td>
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<tr>
<td>Constipation</td>
<td>10 (17.9)</td>
<td>1 (1.8)</td>
<td>5 (13.5)</td>
<td>2 (5.4)</td>
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<td>Vomiting</td>
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<td>1 (1.8)</td>
<td>10 (27.0)</td>
<td>2 (5.4)</td>
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<tr>
<td>Abdominal pain</td>
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<td>1 (1.8)</td>
<td>6 (16.2)</td>
<td>4 (10.8)</td>
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<td>Anorexia</td>
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<td>10 (27.0)</td>
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<td>Arthralgia</td>
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<td>3 (8.1)</td>
<td>1 (2.7)</td>
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<td>Hyperglycemia</td>
<td>8 (14.3)</td>
<td>4 (7.1)</td>
<td>8 (21.6)</td>
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<td>Dyspnea</td>
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<td>6 (16.2)</td>
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<td>Rash</td>
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<td>4 (10.6)</td>
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<td>Muscle spasms</td>
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<td>4 (10.8)</td>
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<td>Musculoskeletal pain</td>
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<td>1 (1.8)</td>
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<td>4 (10.8)</td>
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<td>Decreased appetite</td>
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<td>5 (13.5)</td>
<td>0</td>
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<tr>
<td>Vision blurred</td>
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<td>0</td>
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<td>Dysgeusia</td>
<td>0</td>
<td>0</td>
<td>5 (13.5)</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE: Patients reporting more than one adverse event within a preferred term or a system organ class were only counted once for that preferred term or system organ class.

Abbreviations: AE, adverse event; arm A, cixutumumab + antiestrogen; arm B, cixutumumab; N, number of patients for each treatment; n, number of patients per category for each treatment; TEAE, treatment-emergent adverse event.

(Table 3). There were 3/56 (5.4%) AEs with an outcome of death in arm A and 2/37 (5.4%) in arm B, none of which were study drug related.

Correlative analyses of IR-A, IR-B, and IGF-1R mRNA expression levels in tumor tissue

A majority of the tissue specimens were taken from primary tumor tissue (90%); the remaining samples were biopsied from metastatic lesions. The distributions of mRNA gene expression levels IGF-1R, IR-A, and IR-B are provided in Supplementary Table S2. The mean IR-A expression was higher than the mean IR-B and IGF-1R expression (mean copies/ng RNA: IR-A = 287.3, IR-B = 65.5, and IGF-1R = 12.2).

Cox regressions were performed to correlate each mRNA gene expression dichotomized at the 25th, median, and 75th percentile cutoff points to OS and PFS (Table 3). There were 3/36 (8.3%) AEs with an outcome of death in arm A and 2/37 (5.4%) in arm B, none of which were study drug related.

arm A, patients with low expression of total IR, IR-A, and IR-B had longer PFS and OS than patients with high expression (Fig. 3; Supplementary Table S3; Supplementary Figs. S1 and S2; significant for OS; P = 0.0154, P = 0.0154, and P = 0.0031 for total IR, IR-A, and IR-B, respectively). The correlative analysis results for the 25th percentile and median cutoff points were similar to those for the 75th percentile cutoff point in terms of the direction of HR comparing high to low expression; however, these results were not statistically significant (Supplementary Table S4).

Discussion

The objective of this phase II trial was to analyze the antitumor efficacy of cixutumumab in combination with antiestrogen (arm A) or as cixutumumab monotherapy (arm B) in patients with hormone receptor–positive advanced or metastatic breast cancer that progressed on prior antiestrogen therapy. Furthermore, we also studied the biomarkers that may be associated with clinical efficacy of anti–IGF-1R antibody in hormone receptor–positive breast cancer.

In our trial, cixutumumab administered at 10 mg/kg every 2 weeks with or without antiestrogen therapy did not demonstrate significant clinical efficacy in the ITT population. The median PFS was 2.0 and 3.1 months for arm A and arm B, respectively, which indicates that this analysis is at the first or second disease assessment. Effective progression could have come earlier, but would have been asymptomatic; otherwise, the patient would have discontinued treatment for symptomatic disease progression. The 6-month PFS rates were 20.1% (arm A) and 15.2% (arm B). Although there was a shorter PFS in the combination arm in the...
ITT population, the data were very heterogeneous. These data are in alignment with the efficacy data demonstrated by another IGF-1R blocking therapy (30). In a phase II trial, Robertson and colleagues showed that ganitumab, a monoclonal IgG1 antibody that blocks IGF-1R, in combination with endocrine treatment in a similar patient population, did not improve the primary endpoint of PFS (median PFS, 3.9 months for ganitumab plus endocrine therapy and 5.7 months for placebo plus endocrine therapy; HR, 1.17; P = 0.44; ref. [30]). Limitations of our trial include the lack of an appropriate control arm and the small sample size in arm B, which did not permit relevant statistical analyses.

In the current trial, cixutumumab with or without antiestrogen had an acceptable safety profile. In the safety population, a lower number of patients in arm A (22/56 [39.3%]) experienced grade \( \geq 3 \) AEs than in arm B (19/37 [51.4%]). Overall, the most frequently reported grade \( \geq 3 \) AEs were fatigue, nausea, abdominal pain, and hyperglycemia (5/93 [5.4%] for each). The safety, tolerability, and AE profile of cixutumumab were consistent with the safety profile in previous publications, including fatigue, diarrhea, mild skin toxicities, and hyperglycemia (31–33). Overall, six patients from arm A, and two patients from arm B discontinued treatment due to AEs.

In addition to investigating clinical outcomes of modulating IGF pathways, this trial also analyzed biomarkers that might be predictive of clinical efficacy of cixutumumab in patients with breast cancer. Besides active IGF signaling, the overexpression of IR and IGF-1R in breast cancer tissue compared with normal tissue was involved in tumor growth and progression (12, 13, 18, 34, 35). A number of preclinical trials and clinical correlative analyses have found a prognostic value of IGF signaling in breast cancer (36, 37). In women with node-negative breast cancer, both undetectable and very high levels of IR expression were associated with reduced disease-free survival (38). Law and colleagues demonstrated that phosphorylated IGF-1R and IR are present in all breast cancer subtypes, and along with total levels of IR, are prognostic factors for poor survival (39). IR-A is the predominant IR isoform in breast cancer cells, suggesting that IGF signaling may be mediated by this IR isoform (40).

In this trial, we observed an association between efficacy and baseline tumor-specific IR expression, but not IGF-1R expression. Due to the small sample size of arm B, correlative analyses of IGF-1R, total IR, IR-A, and IR-B mRNA expression were performed on the pooled group from arms A and B (n = 59) and on arm A alone (n = 40). Notably, a significant association was observed between low mRNA expressions of IR-A, IR-B, and total IR and longer PFS and OS in the pooled group using the 75th percentile cutoff point. The correlation between total IR expression and OS should be interpreted with caution, as there was a high censoring of OS. Another limitation was that the study design did not allow us to discriminate between the prognostic and predictive value of IR. Additionally, samples were not taken in this study to determine the level of sustained pathway blockade. However, evidence...
of IGF-1R blockade has been seen with elevated serum levels of IGF-1 and IGFBP-3 in studies using similar doses of cixutumumab (41–44).

In conclusion, this trial did not meet the primary efficacy endpoint of PFS in the ITT population. Clinical outcomes of PFS for both arms A and B were similar or inferior to historical standards (2.0 and 3.1 months vs. 3 months, respectively), but were much lower than the desirable PFS of ≥4.4 months, which was worthy of further investigation (45). As the study did not meet the primary objective, no further investigation is warranted. The results from our correlative studies suggest an association between the expression of IR-A, IR-B, and total IR with both PFS and OS. Clinical validity of total IR and IR isoforms as potential biomarkers predictive of antitumor efficacy of IGF-1R-targeted therapies is yet to be established.

Disclosure of Potential Conflicts of Interest

P. Haluska reports receiving speakers bureau honoraria from Boehringer Ingelheim, is a consultant/advisory board member for Boehringer Ingelheim, Bristol-Myers Squibb, and Medimmune, and reports receiving commercial research support from Bristol-Myers Squibb, ImmClone, and Medimmune. No potential conflicts of interest were disclosed by the other authors.

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References


Phase II Trial of Anti-IGF-1R for Advanced Breast Cancer


Clinical and Translational Results of a Phase II, Randomized Trial of an Anti–IGF-1R (Cixutumumab) in Women with Breast Cancer That Progressed on Endocrine Therapy

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