The Effects of Neoadjuvant Anastrozole and Tamoxifen on Circulating Vascular Endothelial Growth Factor and Soluble Vascular Endothelial Growth Factor Receptor 1 in Breast Cancer

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Abstract

Purpose: Vascular endothelial growth factor (VEGF) is a key angiogenic factor mediating neovascularization. Soluble VEGF receptor 1 (sVEGFR-1) is an intrinsic negative counterpart of VEGF signaling and the ratio of sVEGFR-1 to VEGF has been shown to be a prognostic factor. Estrogen-bound estrogen receptor enhances VEGF expression, providing a common link between these signaling pathways that may be targeted by endocrine therapy. We investigated the effects of anastrozole and tamoxifen over time on serum VEGF and sVEGFR-1.

Experimental Design: The Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) trial compared the preoperative use of anastrozole with tamoxifen in postmenopausal women with estrogen receptor–positive primary operable breast cancer over 12 weeks. Circulating VEGF and sVEGFR-1 were measured by ELISA in 106 patients treated with anastrozole or tamoxifen alone at baseline and after 2 and 12 weeks of treatment.

Results: The increase in serum VEGF from baseline to 12 weeks was significantly different between anastrozole and tamoxifen (anastrozole versus tamoxifen, 6% versus 38%; P = 0.047). There was a significant increase in sVEGFR-1 levels after 12 weeks of anastrozole (P = 0.037). The sVEGFR-1/VEGF ratio significantly decreased in the tamoxifen arm (P = 0.013) and the change in sVEGFR-1/VEGF ratio from baseline to 12 weeks was significantly different between anastrozole and tamoxifen (anastrozole versus tamoxifen, 24% increase versus 34% decrease; P = 0.013).

Conclusions: Treatment with anastrozole and tamoxifen resulted in differential effects on serum angiogenic markers. This may be related to the relative effectiveness of the treatments. These data provide further support for cross talk between estrogen receptor and VEGF.

More than 70% of breast tumors express the estrogen receptor and require estrogen stimulation for their growth. As a result, these tumors are susceptible to endocrine treatment with agents such as tamoxifen and aromatase inhibitors. However, a significant proportion of breast cancers do not respond to these agents and endocrine resistance remains a challenge in the clinic (1). Although third-generation aromatase inhibitors seem to have greater efficacy than tamoxifen in early and late hormone receptor–positive breast cancer (2), the molecular determinants of this differential efficacy are not fully understood. Moreover, the precise mechanisms of endocrine resistance remain unclear.

Angiogenesis, the formation of new blood vessels, is a hallmark of tumor growth and metastasis (3). This complex process is mediated by a host of angiogenic factors of which vascular endothelial growth factor (VEGF) is thought to be pivotal (4). Targeting VEGF with bevacizumab, in combination with chemotherapy, prolonged progression-free survival in a phase III trial of metastatic breast cancer (5). Many tumor cells express VEGF receptors such that VEGF not only acts as a paracrine factor stimulating endothelial cells but also has a direct autocrine action on tumor cells, promoting growth and possibly acting as a survival factor for tumor cells. VEGF-A actions are mediated by binding to Flt-1 (VEGFR-1) and KDR (VEGFR-2). Despite the fact that VEGFR-1 has a higher affinity for VEGF-A, this protein functions as a decoy receptor modulating availability of VEGF to VEGFR-2, the principal receptor thought to mediate the effects of VEGF-A (4). A naturally occurring, alternatively spliced soluble form of VEGF-A (sVEGFR-1) is also expressed in breast cancer (6,7) and a raised ratio of sVEGFR-1 to VEGF predicts a good prognosis (6,8).
the measurement by ELISA of circulating angiogenic markers in blood, which can be obtained at different time points in a reproducible fashion. There are no studies measuring serum sVEGFR-1 in breast cancer, but tumor cytosolic sVEGFR-1/VEGF ratio has been shown to be a potential prognostic marker in breast cancer (6, 8). Several clinical studies have provided evidence for a link between hormone-dependent breast cancer and the VEGF pathway (9–13). There are studies of angiogenic markers and tamoxifen therapy; however, investigations of angiogenic markers following aromatase inhibitor therapy have not been done; this is important given the greater efficacy and consequent increased usage of these aromatase inhibitors. The effect of aromatase inhibitors on serum angiogenic markers in healthy, postmenopausal women also needs to be established.

The Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) trial was a double-blind, randomized, neoadjuvant comparison of anastrozole with tamoxifen alone or in combination in postmenopausal women with estrogen receptor–positive primary breast cancer (14). Although there was no overall difference in response rates between the treatment arms, suppression of Ki67, a marker of proliferation, was greater with anastrozole than tamoxifen at both 2 and 12 weeks (15). On-treatment Ki67 levels in this neoadjuvant setting were subsequently shown to predict recurrence-free survival (16). Serum samples from the IMPACT trial provided a unique opportunity to compare the biological effects of these agents on angiogenic markers over time and to assess any correlation with clinical response of primary breast cancer to endocrine therapy. Similarly, serum from the Letrozole Intermediate Tissue Marker Study (LITMaS) trial, a pilot study evaluating the aromatase inhibitor letrozole for breast cancer prevention (17), provided samples for the analysis of the effects of an aromatase inhibitor on circulating angiogenic markers in healthy, postmenopausal women. The aims of this study were to establish whether serum VEGF and sVEGFR-1 were altered during neoadjuvant treatment with anastrozole or tamoxifen, whether any changes observed differed across the treatment arms, and whether any changes were related to clinical response. The studies were expected to provide further evidence for or against a link between the estrogen receptor and VEGF pathways.

Patients and Methods

Study designs

IMPACT. This was a randomized, double-blind, double-dummy multicenter trial in which patients with primary breast cancer were randomized 1:1:1 to receive a daily dose of anastrozole (1 mg) and tamoxifen placebo (anastrozole arm), tamoxifen (20 mg) and anastrozole placebo (tamoxifen arm), or a combination of tamoxifen (20 mg) and anastrozole (1 mg; combination arm) for 12 weeks before surgery (14). The trial was designed to be the neoadjuvant equivalent of the adjuvant ATAC trial (18). Eligible patients were postmenopausal women with previously untreated, core-needle biopsy proven, invasive, estrogen receptor–positive breast cancer that was operable or potentially operable after medical downstaging and without evidence of metastatic spread. Women were defined as being postmenopausal if they were >60 yr of age; had undergone a bilateral oophorectomy; were <60 yr of age, had a uterus, and had been amenorrheic for at least 12 mo; or were <60 yr of age, did not have a uterus, and had follicle-stimulating hormone levels >20 units/L. Estrogen receptor status was assessed locally and subsequently confirmed centrally (Academic Department of Biochemistry, Royal Marsden Hospital, London, United Kingdom). Any women receiving hormone replacement therapy were required to have ceased such therapy at least 4 wk before the start of trial treatment to be assessable for biomarker end points. The primary clinical objective of the IMPACT trial was to compare the differences between the treatments in objective tumor response. Tumor size was assessed by bidimensional caliper measurement at baseline and before surgery at 12 wk. Objective clinical response was calculated based on WHO criteria. Written informed consent was obtained from all patients before study entry. Patients were recruited between October 1997 and October 2002. Further clinical aspects of the trial are described in detail elsewhere (14). Change in Ki67 was a secondary end point of the IMPACT trial and staining for Ki67 has previously been described (15). Venous blood samples were collected at baseline and at 2 and 12 wk posttreatment from patients receiving either anastrozole or tamoxifen in the IMPACT trial. The samples were allowed to clot at room temperature and centrifuged for 10 min at 2,000 rpm before the serum was separated and stored at −70°C until analysis.

LITMaS study. This was a pilot nonrandomized study for breast cancer prevention that evaluated the effects of letrozole on a series of end points in postmenopausal women without active breast disease. The primary objective of the study was the effect of letrozole on Ki67. Thirty-two volunteers received daily oral letrozole (2.5 mg) for 12 wk. Eligible patients were required to have stopped hormone replacement therapy for >3 mo before study entry. Written informed consent was obtained from all participants before study entry (17). Further details of the study are published elsewhere. Venous blood samples were collected at baseline and 12 wk after letrozole treatment from healthy women in the LITMaS trial and were handled and stored as above.

Measurement of circulating VEGF and sVEGFR-1. Serum samples were analyzed for VEGF and sVEGFR-1 with the use of commercially available ELISA kits (R&D Systems). The ELISA kit used to measure VEGF was specific for the VEGF165 isoform, which is known to play a pivotal role in angiogenesis (4, 19). The measurements were conducted according to the manufacturer’s instructions. The minimum detectable levels of VEGF and sVEGFR-1 were 9 and 3.5 pg/mL, respectively. All samples were assayed in duplicate and the mean of the values was calculated. The intra-assay coefficients of variation for VEGF and sVEGFR-1 ranged from 1% to 10% and 2% to 16%, respectively.

Statistical analysis

The primary analysis was the comparison of circulating VEGF and sVEGFR-1 variables from the anastrozole and tamoxifen groups. The data were log transformed and differences analyzed using Kruskal-Wallis or Mann-Whitney tests to compare between groups. The Wilcoxon signed rank test was used when examining for significant changes. Kruskal-Wallis, ANOVA, Mann-Whitney, Pearson’s correlation, χ², and Student’s t tests were used as appropriate to investigate subgroups and relationships between the angiogenesis variables and other variables. Statistical analyses were done using SPSS for Windows and Insightful S-PLUS. P < 0.05 was considered statistically significant. All patients were included in the overall analysis.

Results

Patient and tumor characteristics. Paired serum samples were available from 28 healthy, postmenopausal women from the LITMaS study. The average age was 60 years (range, 50-78 years). Serum samples were available from 106 patients who were treated with anastrozole (n = 54) or tamoxifen (n = 52) alone and entered into the IMPACT trial. Samples from the combination arm were not analyzed. The baseline characteristics are shown in Table 1. Previous studies have suggested that serum VEGF levels are a measure of VEGF release from platelets during the clotting process and are therefore influenced by the platelet number (20). Platelet counts at baseline and after
12 weeks of endocrine treatment were available for a subset of patients from the IMPACT study (15%; anastrozole, n = 9; tamoxifen, n = 7). There were no significant differences between platelet number at baseline (anastrozole: mean, 302.6/mm³; SD, 57.9; tamoxifen: mean, 297.4/mm³; SD, 90.4) and 12 weeks (anastrozole: mean, 290.2/mm³; SD, 54.4; tamoxifen: mean, 276.3/mm³; SD, 65.9) in either the anastrozole-treated (P = 0.38) or tamoxifen-treated (P = 0.35) group. Although the sample numbers are small, the results suggest that changes in platelet number following endocrine treatment do not account for any changes in serum VEGF.

Serum VEGF and sVEGFR-1 levels do not change with aromatase inhibitor therapy in healthy, postmenopausal women. To examine the possibility that aromatase inhibitors affect serum VEGF and sVEGFR-1 in healthy postmenopausal women, serum samples from the LITMaS study taken at baseline and after 3 months of letrozole treatment were analyzed. There was a wide variability in the baseline levels of VEGF and sVEGFR-1 (VEGF: geometric mean, 368.1 pg/mL; interquartile range, 302.2-510.1 pg/mL; sVEGFR-1: geometric mean, 89.2 pg/mL; interquartile range, 68.1-120.8 pg/mL) but levels in individuals remained stable over the 3 months of aromatase inhibitor treatment with no significant change in either VEGF or sVEGFR-1 (P = 0.97 and P = 0.81, respectively; Fig. 1A and B). Serum levels of estradiol decreased in all of the patients from the LITMaS study included in this analysis, showing good pharmacologic effectiveness and compliance. These results suggest that endocrine treatment with an aromatase inhibitor does not alter the level of serum VEGF or sVEGFR-1 in healthy women and that any changes seen in the IMPACT study in which women have primary breast cancer are likely to be indicative of a tumor effect.

Serum VEGF levels increase after 12 weeks of tamoxifen. Serum VEGF was measured at baseline and after 12 weeks of treatment of patients in the IMPACT trial (Fig. 2A-C). A similar wide variation in baseline levels (geometric mean, 274.3 pg/mL; interquartile range, 182.3-536.3 pg/mL) was shown as in the healthy women and the baseline levels were not significantly different from those in the healthy women (P = 0.18). There was no significant difference at baseline in mean serum VEGF levels between the treatment groups (anastrozole, 312.4 pg/mL; tamoxifen, 239.7 pg/mL; P = 0.62). For most patients, VEGF levels seemed to be stable over 12 weeks but some showed increased levels particularly with tamoxifen (Fig. 2B). No statistically significant changes were seen after 2 weeks of treatment (data not shown) but a significant increase in VEGF levels between baseline and 12 weeks occurred with tamoxifen but not with anastrozole (38% increase; P = 0.006). The change in serum VEGF from baseline to 12 weeks was significantly different between anastrozole and tamoxifen (anastrozole versus tamoxifen: 6% versus 38% increase; P = 0.047; Fig. 2C). One patient had an almost 10-fold increase in VEGF after 12 weeks of tamoxifen. This patient had a tubulo-lobular form of invasive carcinoma and had progressive disease during therapy. The tumor area increased from 6.25 cm² at baseline to 10.08 cm² after 12 weeks of tamoxifen (increase of 61%). The Ki67 increased 16-fold (0.2-3.2%) and there was no change in apoptosis over this time period.

Serum sVEGFR-1 levels increase after 12 weeks of anastrozole. Serum levels of the decoy receptor sVEGFR-1 were measured in

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**Table 1. Baseline characteristics of patients from the IMPACT trial**

<table>
<thead>
<tr>
<th></th>
<th>Anastrozole</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>70 (54-90)</td>
<td>71 (51-88)</td>
</tr>
<tr>
<td>Tumor diameter (cm) at baseline, median (range)</td>
<td>4 (1-7.2)</td>
<td>3.5 (2.5-10)</td>
</tr>
<tr>
<td>ER positive, % of patients</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Patients recorded as previously received HRT, %</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Patients recorded as having had a hysterectomy, %</td>
<td>22</td>
<td>23</td>
</tr>
</tbody>
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Abbreviations: ER, estrogen receptor; HRT, hormone replacement therapy.
the same series (Fig. 3A-C). A similar wide variation in baseline levels was shown as in the healthy women (geometric mean, 98.3 pg/mL; interquartile range, 70.6-141.6 pg/mL) and baseline sVEGFR-1 levels were not significantly different from the healthy women ($P = 0.48$). There was no significant difference at baseline (tamoxifen, 96.9 pg/mL; anastrozole, 99.8 pg/mL; $P > 0.1$) in mean serum sVEGFR-1 levels between the treatment groups, and in keeping with the VEGF analyses, no significant change in sVEGFR-1 was seen after 2 weeks of therapy. For the majority of patients, sVEGFR-1 levels seemed to be stable over 12 weeks but some showed changes. It is notable that a significant increase in sVEGFR-1 levels between baseline and 12 weeks was seen with anastrozole but not with tamoxifen ($P = 0.037$). There was a trend toward significance for the change in serum sVEGFR-1 from baseline to 12 weeks between anastrozole and tamoxifen (anastrozole versus tamoxifen: 32% increase versus 11% decrease; $P = 0.06$; Fig. 3C).

$sVEGFR-1/VEGF$ ratio decreases after 12 weeks of tamoxifen. The ratio sVEGFR-1/VEGF may give a clearer indication of the relationship between VEGF and sVEGFR-1 and better reflect the bioactivity of VEGF (6, 8). There was a significant decrease in sVEGFR-1/VEGF levels between baseline and 12 weeks with tamoxifen but not with anastrozole ($P = 0.037$). There was a trend toward significance for the change in serum sVEGFR-1 from baseline to 12 weeks between anastrozole and tamoxifen (anastrozole versus tamoxifen: 32% increase versus 11% decrease; $P = 0.06$; Fig. 3C).

Relationship between VEGF and sVEGFR-1 and clinical response. In view of the wide variation in baseline VEGF and sVEGFR-1, we then considered whether baseline serum markers were associated with clinical response. Interestingly, within the tamoxifen-treated group, there was a trend toward a significant association between baseline VEGF levels and clinical response (Fig. 5A; $P = 0.051$). Tamoxifen-treated patients with higher baseline VEGF levels were more likely to have a clinical response than patients with lower VEGF levels. However, within the anastrozole-treated group, baseline VEGF levels showed no significant correlation with clinical response, rather, baseline sVEGFR-1 was significantly associated with nonresponders (Fig. 5B; $P = 0.049$). There were no significant correlations between clinical response following anastrozole or tamoxifen and changes in serum VEGF, sVEGFR-1, or sVEGFR-1/VEGF from baseline to 12 weeks.

Relationship between serum angiogenic factors and Ki67. We next considered whether an increase in the proliferation marker Ki67 was positively associated with VEGF or inversely correlated with sVEGFR-1 after 12 weeks of endocrine treatment. In these exploratory analyses, no such correlations were seen.

Discussion

The aim of this study was to investigate the effects of endocrine therapy on angiogenic markers in a neoadjuvant, randomized trial. Although the relationship between VEGF
and tamoxifen has previously been explored in various other clinical settings, the effects of aromatase inhibitors on angiogenesis and a comparison of these effects with tamoxifen have not been studied. Serial blood samples from the neoadjuvant IMPACT trial allowed analyses of changes in circulating VEGF and sVEGFR-1 following anastrozole or tamoxifen over time.

In this study, treatment with anastrozole and tamoxifen resulted in differential effects on serum angiogenic markers. Following 12 weeks of tamoxifen, serum VEGF levels were significantly higher compared with pretreatment levels but anastrozole treatment had no significant effect on VEGF. The change in serum VEGF over 12 weeks was significantly different between the treatments, suggesting that endocrine therapy with aromatase inhibitors and tamoxifen may influence angiogenesis in different ways. Further evidence for this is provided by analysis of serum sVEGFR-1 levels. sVEGFR-1 was significantly higher than pretreatment levels after 12 weeks of anastrozole. Tamoxifen treatment led to a decrease in sVEGFR-1 levels, although this was not significant. The change in serum sVEGFR-1 over 12 weeks of treatment was also significantly different between anastrozole and tamoxifen. There is preclinical evidence that VEGF may be regulated by estrogen at a transcriptional level, and possible mechanisms include an imperfect estrogen response element on the VEGF promoter (21–23). In addition, estradiol increases the extracellular levels of VEGF in both in vitro and in vivo breast cancer models (7, 24). Therefore, by reducing estradiol levels, anastrozole treatment may suppress VEGF production. Tamoxifen has partial agonist and antagonist functions and, unlike anastrozole, does not alter estradiol levels. The increase in VEGF levels seen in this study may be due to the agonist action of tamoxifen. Preclinical studies have also shown an increase in VEGF levels following tamoxifen, supporting this theory (21, 23). It is also possible that tamoxifen lowers VEGF levels via an antagonistic mechanism, but to a lesser degree than seen with estrogen deprivation through aromatase inhibition.

The contrasting changes in VEGF and sVEGFR-1 are not surprising given the biological function of sVEGFR-1. This protein acts as a decoy receptor effectively modulating the bioavailability of VEGF. Therefore, the changes in the ratio of sVEGFR-1/VEGF were of particular interest. There was a highly significant decrease in the ratio after 12 weeks of tamoxifen and an increase with anastrozole, which failed to reach statistical significance. A low sVEGFR-1/VEGF ratio has been associated with poor prognosis in breast cancer (6, 8), and therefore these results may help explain the differential efficacies of aromatase inhibitors and tamoxifen. Given the absence of a no treatment arm, it is not possible to assess directly whether tamoxifen treatment causes an increase in VEGF or whether tamoxifen suppresses VEGF to a smaller degree than does anastrozole.

It is noteworthy that, in contrast to changes in Ki67 seen after 2 weeks of therapy, no significant changes in serum VEGF or sVEGFR-1 were seen after 2 weeks. Importantly, a decrease in

![Fig. 3. Analysis of serum sVEGFR-1 levels in postmenopausal women with estrogen receptor-positive breast cancer from the IMPACT trial. Serum sVEGFR-1 levels were measured by ELISA at baseline and 12 wk posttreatment. A, serum sVEGFR-1 increased significantly after 12 wk of anastrozole (32%; \( P = 0.037 \)). Values from individual patients are expressed as log_{10}. B, sVEGFR-1 levels did not change significantly following tamoxifen treatment. Values from individual patients are expressed as log_{10}. C, mean percentage change (±95% confidence interval) in serum sVEGFR-1 from baseline to 12 wk after either anastrozole or tamoxifen treatment. The change in sVEGFR-1 from baseline to 12 wk between anastrozole and tamoxifen showed a trend toward significance (\( P = 0.06 \)). Bars, 95% confidence interval.](https://www.aacrjournals.org/cgi/content/figure/2008/14/9/2660/F3)
Ki67 was also reported in the IMPACT trial, but as with the angiogenic markers, no significant relationship between this marker and clinical response was seen. The lack of association between changes in markers and clinical response may be due to clinical response being an imprecise end point (15). A likely explanation is that, although we have shown that endocrine treatment with anastrozole and tamoxifen has significant effects on angiogenic markers, these changes may not be sufficient alone to influence clinical response.

In this study, baseline serum angiogenic markers were shown to correlate with clinical response. Although it is notable that baseline markers varied considerably between the healthy postmenopausal women in the LITMaS study, further studies investigating the relevance of baseline circulating VEGF and sVEGFR-1 in relation to clinical response are warranted. The change in sVEGFR-1/VEGF from baseline to 12 wk was significantly different between anastrozole and tamoxifen (anastrozole versus tamoxifen: 24% increase versus 34% decrease; \( P = 0.013 \)).

Differential effects between anastrozole and tamoxifen have also been reported with respect to Ki67 levels in the IMPACT trial (25). We therefore considered whether changes in circulating angiogenic factors correlated with changes in tumor Ki67 after 12 weeks of endocrine treatment. Our hypothesis was that an increase in Ki67 would be positively associated with an increase in VEGF and inversely correlated with sVEGFR-1. This was not the case. The lack of such correlations, however, is not surprising because VEGF and sVEGFR-1 are unlikely to be the only factors governing tumor proliferation. End points such as recurrence-free survival may be a better indicator of an antiangiogenic effect than clinical response or Ki67 given the role of VEGF signaling in the metastatic process. The number of events in the subset of patients in whom we were able to make measurements of angiogenic factors is unfortunately too few (\( n = 4 \)) to investigate the relationship between changes in the levels of these factors and recurrence-free survival. In summary, these data suggest that endocrine agents may exert their effects via antiangiogenic mechanisms, in addition to the predominant antiproliferative activities.

Overall, the extent to which serum VEGF is related to tumor-derived VEGF remains unclear and several parameters need to be considered when interpreting serum VEGF and sVEGFR-1 changes. Some studies have suggested that VEGF measured in serum samples may be released from platelets following venipuncture. Hence, VEGF levels in plasma may reflect circulating VEGF released by the tumor better than serum (20). However, studies across different tumor types and treatments have shown that serum VEGF measurements are of potential prognostic and predictive value (26–30). In addition, it has been suggested that tamoxifen may affect platelet count
Group trial showed that after 12 months of tamoxifen (ref. 31). In addition, results from the Italian Chemoprevention phase II trial (study 223) of neoadjuvant anastrozole alone or hormone replacement therapy use had been ceased for at least 4 weeks before entry. There was no significant difference in either the number of women that had previously been treated with hormone replacement therapy or the number of women that had undergone a hysterectomy between the anastrozole and tamoxifen groups.

Many clinical trials of targeted therapies currently use a combination approach with established treatments. These data raise the possibility that for patients treated with tamoxifen, the addition of angiogenesis inhibitors may improve outcome by suppressing the elevation in VEGF seen with tamoxifen, thereby reducing angiogenic potential. Treatment with aromatase inhibitors may affect angiogenesis via an E2-dependent mechanism and, therefore, in combination with antiangiogenic therapy, might further improve clinical outcome. These data also suggest that it is important to consider the ability of endocrine agents alone to influence angiogenic markers when evaluating trials of antiangiogenic agents in combination with endocrine therapy.

By showing changes in VEGF and sVEGFR-1 with endocrine treatment, this work provides further support for a link between VEGF and the estrogen receptor pathways. Importantly, we have shown differential effects of anastrozole and tamoxifen angiogenic markers that should be considered when combining these different endocrine agents with angiogenesis-targeted treatments.

Acknowledgments

We thank the IMPACT investigators who participated in this trial.

Fig. 5. Analysis of baseline VEGF and sVEGFR-1 levels with clinical response.

A, baseline VEGF levels and clinical response following tamoxifen treatment in postmenopausal women with estrogen receptor–positive breast cancer from the IMPACT trial. Tamoxifen-treated patients with higher baseline VEGF levels were more likely to have a clinical response than patients with lower VEGF levels (P = 0.051). Values from individual patients are expressed as the natural logarithm, ln.

B, baseline sVEGFR-1 levels and clinical response following anastrozole in postmenopausal women with estrogen receptor–positive breast cancer from the IMPACT trial. Higher baseline sVEGFR-1 levels were associated with nonresponders (P = 0.049). Values from individual patients are expressed as the natural logarithm, ln.

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Anastrozole and Tamoxifen in Breast Cancer

Clinical Cancer Research

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