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A Randomized Trial of Combination Anastrozole plus Gefitinib and of Combination Fulvestrant plus Gefitinib in the Treatment of Postmenopausal Women with Hormone Receptor Positive Metastatic Breast Cancer

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Abstract

INTRODUCTION—EGFR signalling pathways appear involved in endocrine therapy resistance in breast cancer. This trial estimates the antitumor efficacy and toxicity of the EGFR tyrosine kinase inhibitor gefitinib in combination with anastrozole or fulvestrant in postmenopausal hormone receptor positive breast cancer.

METHODS—Subjects with estrogen receptor and/or progesterone receptor positive, metastatic breast cancer were randomized into this phase II study of gefitinib (initial dose was 500 mg orally daily, due to high rate of diarrhea, starting dose was reduced to 250 mg orally daily) with either anastrozole 1 mg daily or fulvestrant 250 mg every 4 weeks. The primary endpoint was clinical benefit (complete responses plus partial responses plus stable disease for 6 months or longer).

RESULTS—141 eligible subjects were enrolled, 72 in the anastrozole plus gefitinib arm, and 69 in the fulvestrant plus gefitinib arm. Anastrozole plus gefitinib had a clinical benefit rate of 44% (95% confidence interval 33%–57%) and fulvestrant plus gefitinib 41% (95% confidence interval 29%–53%). Median progression-free survival was 5.3 months (95% confidence interval 3.1–10.4)

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AUTHOR CONTRIBUTIONS

RWC participated in the design of the trial, acquisition of data, authoring the manuscript, and final approval of the manuscript. AO participated in the design of the trial, acquisition of data, authoring the manuscript, and final approval of the manuscript. TV participated in the acquisition of data, authoring the manuscript, and final approval of the manuscript. HLG participated in the acquisition of data, authoring the manuscript, and final approval of the manuscript. SSB participated in the design of the trial, acquisition of data, authoring the manuscript, and final approval of the manuscript. GWS participated in the design of the trial, acquisition of data, authoring the manuscript, and final approval of the manuscript.

versus 5.2 months (95% confidence intervals 2.9–8.2) for anastrozole plus gefitinib versus fulvestrant plus gefitinib, respectively. Median survival was 30.3 months (95% confidence interval 21.2–38.9+) versus 23.9 months (95% confidence interval 15.4–33.5) for anastrozole plus gefitinib versus fulvestrant plus gefitinib, respectively. In general, the toxicity is greater than expected for single agent endocrine therapy alone.

CONCLUSION—Anastrozole plus gefitinib and fulvestrant plus gefitinib have similar clinical benefit rates in the treatment of estrogen and/or progesterone receptor positive metastatic breast cancer, and the rates of response are not clearly superior to gefitinib or endocrine therapy alone. Further studies of EGFR inhibition plus endocrine therapy do not appear warranted, but if performed should include attempts to identify biomarkers predictive of antitumor activity.

Keywords

Metastatic breast cancer; gefitinib; anastrozole; fulvestrant; randomized phase II

BACKGROUND

Endocrine sensitivity of breast cancer is strongly associated with the presence of estrogen receptor (ER) and/or progesterone receptor (PgR) in the breast cancer cells. For metastatic breast cancers that are ER and/or PgR positive, a wide variety of endocrine therapies may result in control of tumor for prolonged periods of time and with generally low levels of toxicity. However, most initially endocrine sensitive tumors ultimately acquire endocrine resistance and many ER and/or PgR positive breast cancers are de novo endocrine resistant.

Epidermal growth factor receptor (EGFR, erbB-1, HER1) is a transmembrane receptor with an extracellular ligand-binding domain and an intracellular tyrosine kinase domain. The ligand-binding domain binds epidermal growth factor, transforming growth factor- α , and amphiregulin. Ligand binding to the extracellular domain results in dimerization of receptor proteins and activation of the tyrosine kinase domain via autophosphorylation. The activated EGFR tyrosine kinase activates cell signaling pathways including the *ras-raf*-mitogen-activated protein kinase pathway, phosphatidylinositol 3-kinase pathway, and protein kinase Akt.

Preclinical and early clinical evidence suggests that activation of EGFR pathways may be an important mechanism of endocrine resistance to tamoxifen, the aromatase inhibitors, and fulvestrant in breast cancer.[1–6] Inhibitors of EGFR suppress EGFR cell signaling pathways. These inhibitors include the orally bioavailable, small molecule EGFR tyrosine kinase inhibitor gefitinib (ZD1839, Iressa). Approximately 30% of ER and/or PgR positive breast cancers demonstrate EGFR positivity.[7] In a phase II study in subjects with tamoxifen resistant, estrogen receptor positive breast cancer, all the tumors expressed EGFR and treatment with single agent gefitinib was associated with a clinical benefit rate of 53%. [8]

This randomized phase II study was designed to assess the efficacy and toxicity profile of gefitinib in combination with either anastrozole or fulvestrant in postmenopausal women with ER and/or PgR positive, recurrent or metastatic breast cancer unselected for level of EGFR expression.

METHODS

Eligibility

Between September 16, 2003 and May 29, 2007, 148 subjects were enrolled into this multi-institutional, randomized phase II trial performed by the Eastern Clinical Oncology Group

([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00057941) identifier: NCT00057941). Eligible subjects had estrogen and/or progesterone receptor positive, histologically confirmed invasive adenocarcinoma of the breast with measurable recurrent or metastatic disease; were postmenopausal as defined by prior bilateral oophorectomy or ovarian irradiation, no menstrual period for 12 months or longer, and if age 55 or less and on adjuvant tamoxifen within prior 6 months to registration, the estradiol level must have been in the postmenopausal range; had received no more than 2 prior chemotherapy regimens for metastatic disease; had not received prior endocrine therapy for metastatic disease; had not received prior aromatase inhibitor, estrogen receptor down-regulator, or EGFR targeted therapy; had no contraindication to intramuscular injections; were age 18 years or older; had ECOG performance status of 0, 1, or 2; had no known CNS metastases; had adequate hematologic, hepatic, and renal function; were not taking medications likely to alter pharmacokinetics of the study drugs; had no ocular inflammation or infection; and were free from other invasive malignancies for five or more years, except for basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix. All subjects provided signed, informed consent under the auspice of a human subjects review committee.

Treatment

Subjects were centrally randomized, following stratification for prior endocrine therapy and dominant site of disease, to anastrozole 1 mg orally daily plus gefitinib or to fulvestrant 250 mg intramuscularly every four weeks plus gefitinib. A cycle was considered four weeks of treatment. The initial starting dose of gefitinib was 500 mg orally daily, but because of a high rate of diarrhea (19% grade 3) observed in the 12 subjects enrolled on trial, the protocol was modified to use a starting dose of gefitinib of 250 mg orally daily. Subjects continued on protocol treatment until disease progression, unacceptable toxicity, continuing study was felt detrimental to the subject, or withdrawal of consent.

No dose reductions or modifications of anastrozole or fulvestrant were allowed. Subjects experiencing grade 3 or 4 toxicity attributed to gefitinib, had the gefitinib withheld for up to 14 days until the toxicity returned to grade 1 or less. Patients not experiencing resolution of toxicity attributed to gefitinib to grade 1 or less within 14 days had protocol therapy discontinued.

Measurement of Effect

Subjects underwent baseline physical examination with tumor measurements; laboratory evaluation with complete blood counts, protime, partial thromboplastin time, bilirubin, AST, ALT, and creatinine; determination of creatinine clearance; chest x-ray, CT scan of chest, abdomen and pelvis; radionuclide bone scan; and radiographs of bones abnormal on bone scan. Repeat physical examination, assessment of toxicity, tumor measurements by physical examination, and laboratory evaluation were performed every 4 weeks. Radiographic studies abnormal on baseline evaluation were repeated every 12 weeks. Classification of response was based upon the RECIST criteria.[9] Toxicity was graded utilizing NCI Common Toxicity Criteria (CTC) version 2.0.[10]

Statistics

The primary endpoint of this randomized phase II trial is the clinical benefit rate with anastrozole plus gefitinib or fulvestrant plus gefitinib. Clinical benefit is defined as those subjects experiencing a complete response or partial response or stable disease for 6 months or longer. Clinical benefit rate was identified as the primary endpoint of the study because of the high frequency of bone involvement in patients with hormone receptor positive, metastatic breast cancer and yet traditional definitions of response exclude bone as a site of assessable disease. Prior studies have demonstrated that stability of disease for 6 months or

longer in response to endocrine treatment in breast cancer predicts for disease related outcomes similar to those experiencing an objective response.[11–13] Other secondary endpoints were progression-free survival, overall survival, and the toxicities of the two treatment combinations. An additional secondary endpoint is the relationship between tumor biomarkers and efficacy and will be reported separately.

With a planned sixty-eight eligible subjects randomized to each arm, either treatment would be considered worthy of further testing in a phase III trial if 22 or more of the 68 eligible subjects in either arm experience clinical benefit. If the true rate of clinical benefit for this combination was 40%, the probability of observing 22 or more subjects in either arm experiencing clinical benefit was 92% and 10% if the true rate was 25%. Allowing 10% of the subjects to be ineligible, up to 74 subjects could have been randomized to each arm.

Progression-free survival (PFS) was defined as the time from date of randomization to disease progression by RECIST, new second breast primary, or death from any cause without documented progression of disease. Cases with incomplete follow-up or without adequate disease evaluations were censored at the date last documented to be progression free. Overall survival (OS) was defined as time from date of randomization to death from any cause. Subjects alive at last follow-up are censored at the date last known to be alive. The Kaplan-Meier method was used to estimate distributions for progression-free and overall survival.[14] Confidence intervals (CI) for median PFS and survival were calculated using the method of Brookmeyer and Crowley. [15] Consistent with the objectives of the trial and the small sample size, formal comparisons between arms were not made.

RESULTS

Patient characteristics

One hundred and forty-eight subjects were enrolled on trial and 7 subjects were ineligible (4 no measurable disease, 1 continuing endocrine therapy, 1 no metastatic disease, 1 baseline scan not performed prior to randomization). For this analysis, there are thus 141 eligible subjects, 72 treated with anastrozole plus gefitinib and 69 treated with fulvestrant plus gefitinib (Figure 1). Patient and disease characteristics are shown on Table 1. The median number of treatment cycles in the anastrozole plus gefitinib arm is 6 (range 1 – 42) and in the fulvestrant plus gefitinib arm is 6 (range 1 – 47). Reasons for treatment termination in the anastrozole plus gefitinib arm were disease progression 54 (75%), toxicity 7 (10%), death 1 (1%), withdrawal 6 (8%), and other 1 (1%). At time of analysis, 3 subjects (4%) were still receiving treatment.; In the fulvestrant plus gefitinib arm reasons for treatment termination were disease progression 53 (77%), toxicity 9 (13%), death 2 (3%), withdrawal 1 (1%), and other 3 (4%). At time of analysis, 1 patient was still receiving treatment (1%).

Toxicity

Thirty-six percent of subjects experience either grade 3 or 4 toxicity with anastrozole plus gefitinib and 35% with fulvestrant plus gefitinib (Table 2). The most common grade 3 or 4 toxicities were diarrhea and liver function abnormalities which are all known to be associated with anastrozole, fulvestrant and gefitinib treatment. . One patient treated with fulvestrant plus gefitinib experienced fatal respiratory failure and pneumonia possibly related to treatment. In general, the toxicity experience is greater than that expected for single agent endocrine therapy alone.

Efficacy

The clinical benefit rate experienced with anastrozole plus gefitinib was 44% (95% confidence interval 33%–57%; CR 3%, PR 22%, SD for ≥ 6 months 19%) and with

fulvestrant plus gefitinib was 41% (95% confidence interval 29%–53%; CR 4%, PR 16%, SD for ≥ 6 months 20%). At the time of analysis, 125 or the 141 eligible subjects had experienced a progression event and 85 subjects had died. Kaplan-Meier progression-free survival curves and overall survival are shown in Figure 2. Median PFS (95% CI) was 5.3 months (3.1–10.4) for anastrozole plus gefitinib and 5.2 months (2.9–8.2) with fulvestrant and gefitinib. In patients who had received prior chemotherapy for metastatic disease, median PFS was 6.4 months (95% CI = 2.3–15.1) with anastrozole plus gefitinib and 2.6 months (1.5–8.2) with fulvestrant and gefitinib. There was no difference in progression free survival among those patients with a disease free interval (DFI) of 24 months or less or among those with a DFI greater than 24 months.

Median survival (95% CI) was longer at 30.3 (21.2–38.9+) months for anastrozole plus gefitinib compared with 23.9 months (15.4–33.5) for fulvestrant and gefitinib. However, the study was not designed to directly compare overall survival, and no test of statistical significance if thus provided. We do not have details of subsequent treatment to assess if differences in post protocol treatment could explain the overall survival differences.

DISCUSSION

Our results document activity of combination anastrozole plus gefitinib and of fulvestrant and gefitinib. The phase II nature of this trial does not allow the assessment of the antitumor activity provided by gefitinib alone, endocrine therapy alone, or the combination of gefitinib plus endocrine therapy. There was a 35% frequency of Grade 3–4 toxicity in this trial, therefore the safety profile of the combinations was less favourable than that expected with any of the agents alone.”

Two randomized studies have compared fulvestrant to anastrozole as second-line endocrine therapy in postmenopausal women with endocrine sensitive advanced breast cancer. A combined analysis of these studies documented a clinical benefit rate with fulvestrant of 43.5% and with anastrozole of 40.9%. [16] As the clinical benefit rate is highly dependent upon patient population, direct comparison of these clinical benefit rates with those experienced in our patient population is difficult and is impacted by differences in patient population, sites of disease, and measurement of effect. However, comparison of these published data with those obtained in the present study suggests no improvement in overall rates of response with the addition of gefitinib to endocrine therapy with fulvestrant or anastrozole.

A recent multi-institutional, double-blind randomized clinical trial compared fulvestrant 500 mg monthly (plus a loading dose) versus 250 mg monthly in postmenopausal women with ER and/or PgR positive or ER and PgR unknown metastatic breast cancer previously untreated with endocrine therapy. [17] This trial demonstrated a statistically significant improvement in progression free survival (hazard ratio 0.80; 95% confidence interval 0.68 – 0.94; $P = 0.006$) with no statistically significant difference in objective response rate, clinical benefit rate, or overall survival. As our trial utilized a dose of fulvestrant 250 mg, it is possible that a high dose would have been associated with an improvement in outcome.

A randomized phase II trial of neoadjuvant anastrozole or anastrozole plus gefitinib in postmenopausal women with hormone receptor positive breast cancer, demonstrated that the addition of gefitinib to anastrozole was not superior to anastrozole alone, with objective rates or response of 48% and 61%, respectively. [18] In another study, 93 postmenopausal women with hormone receptor-positive disease who had not received prior endocrine therapy for metastatic disease were enrolled and randomized on a phase II trial of anastrozole in combination with either gefitinib or placebo. [19] The clinical benefit rate for

anastrozole plus gefitinib was 49% compared with 34% with anastrozole plus placebo. Progression free survival also favored anastrozole plus gefitinib (hazard ratio 0.55; 95% confidence interval 0.32 – 0.94; median progression-free survival 14.7 vs. 8.4 months).

In this study, the clinical benefit rates are 44% (95% confidence interval 33%–57%) with anastrozole plus gefitinib and 41% (95% confidence interval 29%–53%) with fulvestrant plus gefitinib. While our study did not include a gefitinib alone or endocrine therapy alone cohort, these clinical benefit rates are not clearly superior to those with endocrine therapy alone,[20] and are similar to that of gefitinib alone in tamoxifen resistant disease.[8] The limited benefit of adding gefitinib may be related to multiple mechanisms. Only approximately 30% of ER/PgR positive breast cancers over-express EGFR, and those that do tend to be more aggressive and resistant to endocrine therapy. Our subjects were not selected for levels of EGFR expression, and it is possible that the impact of even a highly active endocrine therapy might be missed because of a high proportion of tumors not expressing high levels of EGFR. We do not have information regarding the degree of EGFR inhibition at the dose of 250 mg of gefitinib, and it is possible that more selective and complete inhibition of tumoral EGFR would be more effective. There is also evidence that HER2 expression is associated with endocrine resistance, and gefitinib does not suppress HER2-related signaling.[1, 21–25] Tumor blocks were collected as a part of the current clinical trial, and biomarker assessment is in process to address some of these important questions. Multiple additional questions exist regarding the importance of facilitating or inhibiting various combinations of multiple regulators of signaling pathways including EGFR, HER2, mTOR, ER, PgR and others, and how they interact with each other in clinical outcomes.

Areas for further investigation include the performance of a prospective randomized trial of endocrine therapy alone versus endocrine therapy plus EGFR inhibition using either targeted EGFR inhibition or an inhibitor of multiple growth factor receptors. Important design considerations in such a trial would include determination and stratification of initial EGFR status and outcomes. It could be argued that subjects with an initially increased expression of EGFR would be those most likely to benefit from EGFR inhibition, although it could also be argued that the prevention of acquired endocrine resistance in those with low initial EGFR expression is at least as important. Only prospective clinical trials with assessment of biomarker expression including quantitative ER, PgR, EGFR, and HER2 measurements is likely to further clarify these important considerations.

Based upon the results of this randomized phase II trial, the antitumor activity of anastrozole plus gefitinib and fulvestrant plus gefitinib appears modest, and these combinations have a less favorable safety profile compared to endocrine monotherapy. Further trials of these combinations do not appear warranted.

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Figure 1.
Consort diagram.

Figure 2.
A. Progression-free survival. B. Overall survival.

Table 1

Patient Characteristics n(%) shown

Treatment Arm	Anastrozole + gefitinib	Fulvestrant + gefitinib	Total
Number of subjects	72	69	141
Ethnicity/Race			
Hispanic White	33(46)	30(43)	63(45)
Non-Hispanic white	32(44)	33(48)	65(46)
Non-Hispanic Other	2(3)	2(3)	4(3)
Unknown	5(7)	4(6)	9(6)
Median age in years (range)	58 (34–90)	63 (35–91)	59 (34–91)
ECOG Performance Status			
(0) Fully Active	25(35)	26(38)	51(36)
(1) Ambulatory	45(63)	39(56)	84(60)
(2) Self Care, but not work	2(3)	4(6)	6(4)
Hormone receptor status			
ER-PgR+	2(3)	1(1)	3(2)
ER+PgR–	15(21)	15(22)	30(21)
ER+PgR unknown	3(4)	1(1)	4(3)
ER+PgR+	50(69)	47(68)	97(69)
ER or PgR positive recurrence	2(3)	5(7)	7(5)
Prior adjuvant endocrine therapy	33(46)	29(42)	62(44)
Prior chemotherapy			
Adjuvant only	23(31)	24(35)	47(33)
Metastatic disease only	7(10)	8(12)	15(11)
Adjuvant and metastatic	4(6)	3(4)	7(5)
Disease-free interval			
24 months	32(44)	34(49)	66(47)
>24 months	40(56)	35(51)	75(53)
Sites of Involvement			
Local-regional	43(60)	35(51)	78(55)
Ipsilateral supraclavicular nodes	16(22)	8(12)	24(17)
Opposite Breast	2(3)	6(9)	8(6)
Distant Nodes	22(31)	22(32)	44(32)
Distant skin/tissue	5(7)	8(12)	13(9)
Bone	47(65)	38(55)	85(60)
Bone Marrow	2(3)	3(4)	5(4)
Lung	32(45)	36(52)	68(48)
Liver	25(35)	16(23)	41(29)
Pleura	17(24)	14(20)	31(22)

Treatment Arm	Anastrozole + gefitinib	Fulvestrant + gefitinib	Total
Number of subjects	72	69	141
Other	5(7)	8(12)	13(9)

Table 2

Treatment related Toxicities. Only grade 3 or 4 occurring in 3% or more of either treatment arm are included. All toxicities are worst grade per patient. All subjects receiving treatment are included even if determined ineligible for trial.

Toxicity type	Treatment Arm									
	Anastrozole plus gefitinib (n=74)					Fulvestrant plus gefitinib (n=74)				
	Grade					Grade				
	1,2 (%)	3 (%)	4 (%)	5 (%)		1,2 (%)	3 (%)	4 (%)	5 (%)	
Fatigue	41	3	-	-	-	32	3	-	-	-
Hand-foot reaction	4	3	-	-	-	8	-	-	-	-
Anorexia	24	1	-	-	-	23	4	-	-	-
Dehydration	38	3	-	-	-	41	1	1	-	-
Nausea	27	4	-	-	-	18	4	-	-	-
Vomiting	16	3	-	-	-	11	1	1	-	-
Diarrhea	46	5	-	-	-	45	12	1	-	-
Bilirubin	8	-	3	-	-	18	-	3	-	-
SGOT	30	7	-	-	-	32	7	1	-	-
SGPT	31	4	-	-	-	31	4	-	-	-
Infection w/o neutropenia	9	1	-	-	-	9	3	-	1	-
Arthralgia	9	7	-	-	-	14	-	-	-	-
Hypoxia	-	-	-	-	-	-	3	-	-	-
All toxicities, worst degree (%)	61	31	5	0	58	28	7	1		

Table 3

Best Response n (%) shown

	Anastrozole + gefitinib	Fulvestrant + gefitinib	Total
CR	2(3)	3(4)	5(4)
PR	16(22)	11(16)	27(19)
Stable disease lasting ≥ 6 months	14(19)	14(20)	28(20)
Clinical benefit (CR+PR+SD for ≥6 mos)	32(44)	28(41)	
Stable disease not lasting 6 months	5(7)	7(10)	12(8)
Progression	31(43)	30(43)	61(43)
Unevaluable *	4(6)	4(6)	8(6)
Total	72	69	141

* not on study treatment for minimum interval of 8 weeks required for response evaluation.