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A phase II evaluation of gefitinib in the treatment of persistent or recurrent endometrial cancer: A Gynecologic Oncology Group study ☆

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HIGHLIGHTS

- Gefitinib was evaluated in a phase II trial of advanced endometrial cancer.
- One patient achieved a complete response, though gefitinib did not demonstrate significant clinical activity overall.
- The levels of a soluble truncated form of EGFR, sEGFR, positively correlated with overall survival.

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ABSTRACT

Background. A phase II trial was performed to evaluate the efficacy and safety of gefitinib in patients with persistent/recurrent endometrial cancer.

Methods. Women with histologically confirmed persistent/recurrent endometrial cancer were treated with 500 mg oral gefitinib daily until progression or severe toxicity, with progression-free survival (PFS) at six months as the primary endpoint. Tumor expression of total epidermal growth factor receptor (EGFR), estrogen receptor (ER), progesterone receptor A (PRA) and B (PRB), Ki67, pEGFR and activated extracellular signal-regulated kinase (pERK) were examined pre- and post-treatment. EGFR was sequenced, and serum concentrations of soluble EGFR (sEGFR) at baseline also were examined.

Results. Of 29 patients enrolled, 26 were evaluable for efficacy and toxicity. Four patients experienced PFS ≥6 months, and one had a complete response which was not associated with an EGFR mutation. The concentration of sEGFR in pretreatment serum was positively correlated with overall survival (OS), but not with responsiveness to gefitinib in this small patient cohort. Expression of tumor biomarkers was not associated with PFS or OS. Co-expression of ER with PRA in primary and recurrent tumors, and pEGFR with pERK in primary tumors was observed.

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Conclusions. This treatment regimen was tolerable but lacked sufficient efficacy to warrant further evaluation in this setting. The possible association between serum sEGFR concentrations and OS, and temporal changes in expression of pEGFR and pERK and the documented CR of one patient are interesting and warrant additional investigation.

Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States, with an estimated 47,130 cases and 8010 deaths expected in 2012 [1]. While most patients present with early stage disease and are cured by treatment, the prognosis for patients who relapse is poor, and traditional chemotherapeutic regimens for relapsed patients result in low response rates [2–4]. For these patients, biologically targeted therapeutics are enticing experimental regimens.

The epidermal growth factor receptor (EGFR) is a transmembrane receptor tyrosine kinase that regulates many basic facets of cell and tissue function including cellular growth, survival, differentiation, and migration [5]. EGFR is often overexpressed or mutated in adult solid tumors. Efforts over the last two decades to design EGFR tyrosine kinase inhibitors culminated with FDA approval of the orally active drugs gefitinib and erlotinib for treatment of non small cell lung cancer (NSCLC) and erlotinib for treatment of pancreatic cancer. While methods for stratifying patients most likely to benefit from gefitinib treatment are still being optimized, mutations in EGFR to date appear to be the best predictive marker of responsiveness for NSCLC patients [6]. Moreover, an alternate isoform of EGFR, designated sEGFR, present in both tumor tissue and in circulation, also has been shown to have clinical utility in cancer patients [7–14] and is being studied as a predictive marker of responsiveness to treatment in cancer patients [15].

In vitro and *in vivo* studies of endometrial cancer have implicated EGFR as an important regulator of cell proliferation and survival [16–21]. However, tumor EGFR expression has been associated with adverse outcomes in endometrial cancer only in some studies [19,22–24], whereas in others, EGFR is not a significant marker of survival [25–28]. Serum sEGFR concentrations have not previously been examined in endometrial cancer patients.

Gefitinib has substantial growth inhibitory and apoptotic inductive activity in a number of *in vitro* and *in vivo* studies using tumor cell lines and xenografts, including those of endometrial origin [17,29–33]. Only one study thus far has reported on the efficacy of an EGFR tyrosine kinase inhibitor (i.e. erlotinib) for the treatment of patients with endometrial cancer [34]. Gefitinib is safe and well tolerated with some associated dermatological and gastrointestinal adverse events.

The primary endpoint of this phase II clinical trial was progression-free survival (PFS) at six months for daily oral gefitinib (500 mg) as a treatment for recurrent or persistent endometrial cancer. Overall survival (OS) was included as a secondary endpoint. The potential prognostic and predictive clinical utility of several candidate biomarkers previously associated with steroid receptor and EGFR signal transduction pathways in endometrial cancer were evaluated.

Materials and methods

This was a Gynecologic Oncology Group (GOG) sponsored non-randomized, multicenter phase II open-label trial, designated GOG 229C, which evaluated the efficacy and safety of gefitinib (supplied by AstraZeneca, Cheshire, UK) in 26 evaluable patients with endometrial carcinoma who had persistent or recurrent disease following front-line chemotherapy and higher priority protocols. Clinical and laboratory toxicities were monitored and graded according to the National Cancer Institute Common Toxicity Criteria (CTC) Version 2.0. All adverse events were recorded and graded according to the CTC, Version 2.0 (http://ctep.info.nih.gov). Radiographic studies were performed at two-month intervals. All patients who progressed were followed to assess OS.

Eligibility

Patients with histologically confirmed, recurrent or persistent endometrial carcinoma after at least one chemotherapeutic regimen, and with at least one measurable lesion (at least 20 mm by palpation, X-ray, CT scan, or MRI, or at least 10 mm by spiral CT scan) were eligible for this trial. Each patient provided written consent for the protocol including the translational research component with annual Institution Review Board approval at each of the participating institutions and laboratories in accordance with local, state, and federal regulations and guidelines.

Study design and treatment plan

Gefitinib was administered at a dose of 500 mg per day orally. Each 28 day period was considered a cycle. If side effects were not severe and requirements for monitoring toxicity were met, patients were eligible to remain on the study agent until progression.

Management of toxicity

In general, gefitinib was withheld in patients with grade 2 or greater toxicities until resolution, and patients were then restarted on a reduced dose of 250 mg/day. No dose reductions below 250 mg were allowed. If toxicities did not resolve to grade ≤ 1 or baseline after two weeks of withholding gefitinib (≥ 15 days) for any toxicity, the patient was removed from study.

On-study evaluation

Details are provided in the Supplemental Methods.

Biological samples

Archived formalin-fixed, paraffin-embedded (FFPE) primary tumor tissue from the initial hysterectomy, and serial pre- and post-treatment biopsies (core biopsies or final needle aspirates) of recurrent or persistent tumor were required for this protocol. Patients also were asked to provide serum samples prior to gefitinib treatment. See Supplemental Methods for additional details.

Analysis of EGFR mutation status

Genomic DNA was extracted from FFPE tumor tissue using a TrimGen DNA purification kit (TrimGen Corp, Sparks, MD) according to the kit instructions. EGFR exons 18–21 were amplified by polymerase chain reaction (PCR) as published previously and the amplicons sequenced as described in Supplemental Methods [35].

Analysis of serum sEGFR concentrations

Twenty-four (of 26 evaluable) patients provided baseline serum samples prior to gefitinib treatment for sEGFR quantitation. Serum sEGFR was quantitated by acridinium-linked immunosorbent assay as previously described [36,37].

Analysis of tumor biomarker expression

FFPE archival tumor tissue specimens, either from the primary or the recurrent endometrial tumors, were tested for expression of selected biomarkers in the GOG Core Laboratory for Receptors using previously published immunohistochemical (IHC) methods, as described in Supplemental Methods [38].

Design, end points, and statistical considerations

The primary endpoints of this study included the frequency of patients with PFS for at least six months and the frequency and severity of adverse events. OS, PFS, and response were evaluated as secondary endpoints. Demographical and clinicopathological covariates included patient age, race, performance status, and tumor cell histology. Biomarker covariates included tumor EGFR mutation status, tumor expression of EGFR, phospho-EGFR (pEGFR), estrogen receptor (ER), progesterone receptor A (PRA), progesterone receptor B (PRB), activated (phospho-extracellular-regulated kinase (pERK), and the nuclear cell proliferation protein Ki67, and baseline serum soluble EGFR (sEGFR) concentrations. Primary vs. tumor vs. recurrent tumors were compared for changes in EGFR, pEGFR, ER, PRA, PRB, pERK, and Ki67 expression. Pretreatment baseline sEGFR concentrations were evaluated for associations with PFS and OS.

The study was designed to detect cytostatic activity of gefitinib by examining the proportion of patients with PFS for a period of six months. Historical controls of a similar population of endometrial cancer patients were used to determine an uninteresting proportion of patients with PFS at six months. Based on this analysis, agents that yield a true probability of 15% or less in patients with PFS at six months should be considered unpromising whereas agents capable of inducing 30% or more patients with PFS at six months should be investigated further in phase III studies. A flexible, two-stage group sequential study design by Chen and Ng [39] which had an average 10% level of significance with 90% average power when the true probability was 30% was used to compare the control and gefitinib-treated groups. The specific features of this study design are more fully explained in Schilder et al. [40]. This design required more than four patients with PFS at six months to proceed to the second stage when 26 patients were recruited to the first stage. Had the study proceeded to the second stage, the trial would have targeted 56 patients cumulatively and required at least 12 patients to be PFS at six months before classifying gefitinib as clinically interesting. Potential associations between biomarkers, patient demographics, and clinical outcome (response, PFS at six months, PFS, and OS) were explored using Kendall's or Spearman's correlation coefficient, Fisher's Exact Test, exact Chi-square tests, or Cox proportional hazards models. Any test yielding an unadjusted (for multiple testing) p-value <0.05 was deemed suggestive or notable for the purpose of hypothesis generation in future studies. Any test yielding a p-value between 0.05 and 0.1 was considered a "possible trend." Since the sample size was small with a high degree of missingness, these analyses were unpowered with potential bias; therefore, negative results cannot be interpreted as conclusive.

Results

This phase II study enrolled 29 patients with recurrent or persistent endometrial cancer from 16 participating institutions across the United States from July 2002 to November 2003. Two patients were excluded due to inadequate pathology, and one was excluded because she was misclassified as having endometrial cancer. All of the remaining 26 patients were eligible and evaluable.

Patient characteristics and treatment administration

Table 1 summarizes the patient's demographical and clinicopathological characteristics, therapy, and primary endpoints. Of the eligible and evaluable patients, eight had prior hormonal therapy. Eighteen patients had received prior radiation therapy. Twenty of the 26 patients received more than one cycle of gefitinib monotherapy, and three patients received six or more cycles of gefitinib monotherapy before disease progression. The median number of gefitinib cycles was two.

Toxicity

All eligible patients were evaluable for adverse effects. Table 2 shows the adverse events experienced by patients during the course of gefitinib treatment. Toxicities associated with gefitinib treatment were not excessive within this patient population, with the majority of patients experiencing grade 1 and 2 toxicities. However, several patients experienced grade 3 and grade 4 toxicities. Grade 3 toxicities included the following adverse event categories: gastrointestinal (5), constitutional (5), dermatologic (4), other hematologic (3), pain (3), neurologic (2) anemia (1), cardiovascular (1), metabolic (1), ocular (1), and pulmonary (1). Grade 4 toxicities included the following adverse event categories: anemia (1), neurologic (1), and pain (1). One patient died while on study (cardiopulmonary arrest). This death was not attributable to treatment. No patients were removed from study therapy for toxicity, but two patients refused further therapy.

Objective tumor response

Of the 26 patients who were evaluable for response to gefitinib, two patients were not assessed post-treatment for reasons unrelated to their cancer diagnosis. One patient with a 2 cm vaginal recurrent lesion achieved a complete response (CR) lasting 10.6 months (3.8% with 90% 2-sided CI 0.1–17.0%). Seven patients had disease stabilization. The clinical benefit rate (responders + disease stabilization) was 31% among evaluable patients.

Table 1
Patient characteristics and outcomes.

Characteristic	Number of cases
Age	
30–39	1
40–49	2
50–59	7
60–69	9
70–79	4
80–89	3
Race	
White	24
American Indian	1
Black	1
Performance status (GOG)	
0	14
1	9
2	3
Cell type	
Undifferentiated carcinoma	1
Endometrioid adenocarcinoma	16
Mixed epithelial carcinoma	3
Serous adenocarcinoma	6
Prior chemotherapy regimens	
1	19
2	7
Prior hormone therapy	8
Prior radiotherapy	18
Cycles of treatment	
1	6
2	13
3	1
4	3
6–20	3
Progression-free $\geq$6 months	4 (15.4)
Objective tumor response	
Complete response	1 (3.8)
Stable disease	7 (26.9)
Progressive disease	16 (61.5)
Not evaluable	2 (7.7)

Four of 26 patients (15.3% with 90% 2-sided CI 5.4–31.8%) had PFS at six months following initiation of therapy (see Fig. 1A). At 24 months, three patients survived, each of whom had progressive disease. Median PFS and OS were 1.8 and 7.1 months, respectively.

Mutation analysis of the EGFR tyrosine kinase domain

Twenty patients had archival primary tumor samples positive for EGFR by immunohistochemistry. Genomic sequencing of EGFR exons 18–21, which encode the tyrosine kinase domain, was performed. In one patient, an E709K mutation was observed. This mutation has been described previously in NSCLC patients treated with gefitinib but was not associated with response in this study [41]. The patient with the complete response did not demonstrate an EGFR mutation.

Serum sEGFR biomarker analysis

Serum was obtained from 24 patients prior to initiating gefitinib treatment. In these patients, the median serum sEGFR concentration was 1960 fmol/ml. Patients were dichotomized using the median concentration as a cutoff (i.e. "low sEGFR" <1960 fmol/ml, "high sEGFR" ≥1960 fmol/ml) and assessed for association with response and survival (see Table 3). High vs. low serum sEGFR was not associated with response or PFS in gefitinib-treated patients. Only one patient in the trial had a complete response to gefitinib monotherapy; 0 of 12 patients with low serum sEGFR responded to gefitinib, and 1 of 12 patients with high sEGFR responded to gefitinib. One of 12 patients with low serum sEGFR demonstrated PFS >6 months, and 3 of 12 patients with high serum sEGFR demonstrated PFS >6 months. Patients with high vs. low sEGFR had an indeterminate risk of disease progression (PFS hazard ratio = 0.574, 95% CI 0.245–1.344). However, the hazard ratio of death for patients with high vs. low sEGFR was 0.320 (95% CI: 0.128–0.796), suggesting that patients with high sEGFR had a 68% lower risk of death at a given time point than patients with low sEGFR (Fig. 1B). Patients with high vs. low sEGFR had a median survival of 11.0 months vs. 4.1 months for patients with low sEGFR respectively (Table 3).

Tumor biomarker analyses

Primary and recurrent tumor samples were assessed by immunohistochemistry for expression of EGFR, Ki67, ER, PRA, PRB, activated (phosphorylated) EGFR (pEGFR) and ERK (pERK). Response, PFS, and OS were not associated with expression for any of the tested biomarkers. However, we did note a number of interesting patterns of co-expression (Figs. 2 and 3). Correlations were observed between ER with PRA in primary tumors (Fig. 2A, panel 1; r = 0.586), pre-treatment recurrent tumors (Fig. 2A2; r = 0.780), and post-treatment tumors (Fig. 2A3; r = 0.876). This finding underscores the functional link between ER and PRA and is expected as PR is induced by ER. The positive correlation between ER and PRA in all specimens (original hysterectomy, pre-treatment recurrent and post-treatment recurrent) demonstrates the consistent biologic mechanism underlying the association. A strong correlation between pEGFR with pERK was demonstrated in primary tumors (Fig. 2B1; r = 0.768), which is expected in cases where EGFR is a primary growth factor receptor controlling downstream ERK phosphorylation. A lower correlation coefficient in pre-treatment recurrent cases (r = 0.482) and post-treatment recurrent tumors (r = 0.427) was found. The biological explanation for this is not fully known; however, it could be speculated that in recurrent cases, ERK signaling may be dependent upon other growth factor receptors in addition to EGFR.

Interesting temporal changes in the expression of selected markers were also noted in primary hysterectomy vs. recurrent pre-treatment tumors (Figs. 3 and 4). Specifically, expression of pEGFR and pERK appeared to be higher in many matched recurrent vs. primary tumors (Fig. 3A1 and Fig. 3C1, respectively). Only two of 17 (12%) primary tumors expressed high levels of pEGFR. However, in matched recurrent tumors, 12 of the 15 (80%) tumors expressed high levels of pEGFR. Similarly, four of 17 (24%) primary tumors expressed high levels of pERK, but in matched recurrent samples, nine of these 13 (69%) tumors expressed high levels of pERK. These findings suggest that recurrent tumors may activate this pathway to a greater degree than primary tumors. However,

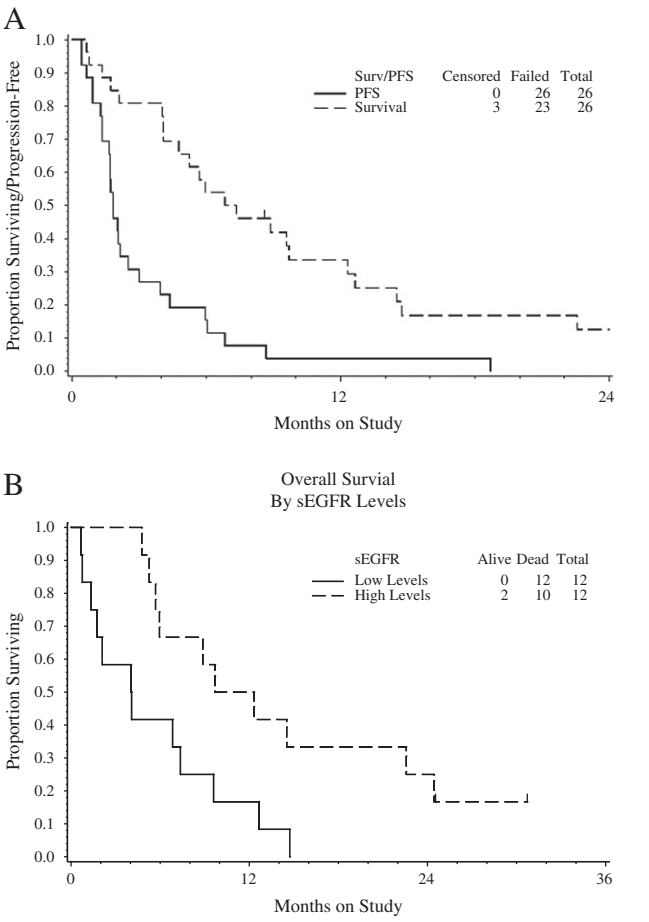

Fig. 1. Progression-free survival and overall survival of endometrial cancer patients receiving single agent gefitinib (A). Kaplan–Meier plot of progression-free survival (solid line) and overall survival (dashed line) is depicted above. By the end of 24 months on the study, all patients had progressed, and three patients were still alive. Overall survival distribution for women with low vs. high pre-treatment serum sEGFR (B).

Table 2
Adverse effects of gefitinib using Common Toxicity Criteria (CTC) Version 2.

Adverse event	Grade					Total
	0	1	2	3	4	
Leukopenia	24	2	0	0	0	26
Thrombocytopenia	20	6	0	0	0	26
Neutropenia	25	1	0	0	0	26
Anemia	7	7	10	1	1	26
Hematologic—other	23	0	0	3	0	26
Cardiovascular	22	2	1	1	0	26
Fatigue	8	4	9	5	0	26
Dermatologic	9	11	2	4	0	26
Gastrointestinal	6	6	9	5	0	26
Hemorrhage	22	3	1	0	0	26
Hepatic	20	5	1	0	0	26
Infection	25	0	1	0	0	26
Musculoskeletal	24	2	0	0	0	26
Metabolic	20	4	1	1	0	26
Neurologic	19	3	1	2	1	26
Ocular	21	2	2	1	0	26
Pain	17	4	1	3	1	26
Pulmonary	24	0	1	1	0	26

Table 3
Association between pre-treatment serum sEGFR concentration and objective tumor response, proportion progression-free ≥6 months, progression-free survival (PFS) and overall survival (OS). sEGFR levels were categorized as low or high.

	Cases	Response		PFS > 6 mon.		Median survival (mon.)	
		No	Yes	No	Yes	PFS	OS
sEGFR							
Low	12	12	0	11	1	1.6	4.1
High	12	11	1	9	3	1.9	11.0
Total	24	23	1	20	4	1.8	6.8

	Cases	Cox modeling			
		PFS		OS	
		HR	95% CI	HR	95% CI
sEGFR					
Low	12	1.00	Referent	1.00	Referent
High	12	0.57	(0.25–1.34)	0.32	(0.13–0.80)

somewhat surprisingly, higher expression of pEGFR was observed in several post- vs. pre-treatment recurrent tumors in which gefitinib treatment would be expected to block pEGFR (Fig. 3A2, Fig. 4).

Discussion

Daily 500 mg gefitinib resulted in a low proportion responding among patients with persistent or recurrent endometrial cancer in this phase II trial. Response rates were lower than those observed in a recent phase II trial of another EGFR tyrosine kinase inhibitor, erlotinib, but the small sample size of both trials makes a direct comparison between these two studies challenging [34]. Though only one patient had a CR to gefitinib monotherapy, it is worth noting that this was an unselected patient population with regard to EGFR status. Four patients exhibited PFS ≥ six months, and seven patients experienced disease stabilization.

Correlations were observed between ER vs. PRA (r = 0.586), and pEGFR vs. pERK (r = 0.768) in primary tumors, and between ER vs. PRA in both pre-treatment (r = 0.780) and post-treatment (r = 0.876) recurrent tumors. While others have demonstrated correlations between ER vs. PR status in endometrial cancer [42–47], correlations between pEGFR vs. pERK have not been previously reported. This study also compared pEGFR and pERK expression in the original hysterectomy specimen vs. pre-treatment and post-treatment tumor specimens. Increased expression of pEGFR and pERK was noted in pre-treatment recurrent vs. primary hysterectomy tumor specimens, supporting the primary hypothesis that EGFR/ERK signaling is activated during disease

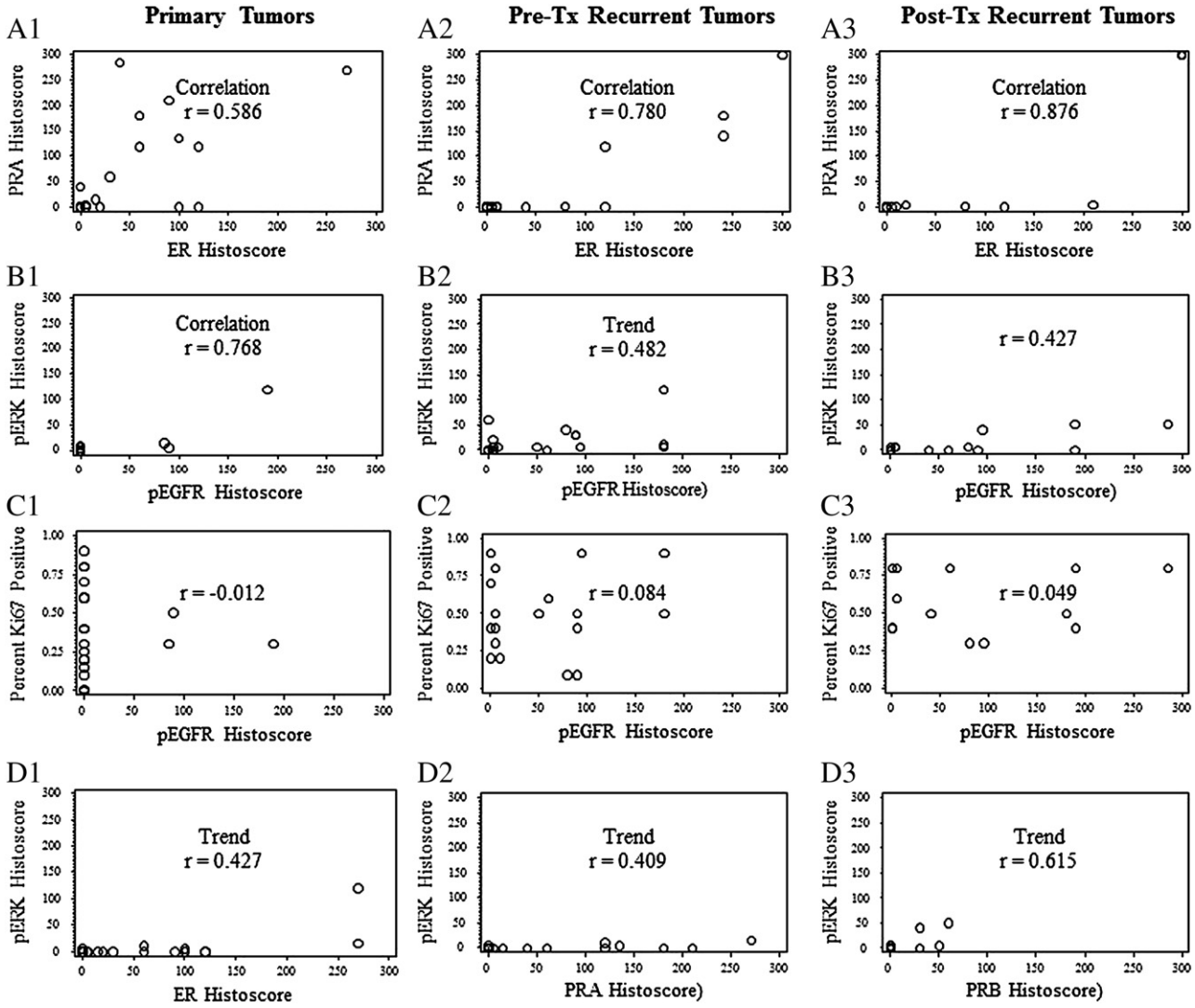

Fig. 2. Relationship between expression of ER and PR (A1–A3), pEGFR and pERK (B1–B3), pEGFR and Ki67 (C1–C3), and pERK and steroid receptors (D1–D3) in primary tumors (A1, B1, C1, D1, D2), pre-treatment (Pre-Tx) recurrent tumors (A2, B2, C2), and post-treatment (Post-Tx) recurrent tumors (A3, B3, C3, D3). ER, PRA, PRB, pEGFR, and pERK were expressed as a histoscore (aggregate of percent of positive tumor cells and staining intensity). Ki67 was expressed as a percent of Ki67 positive tumor cells.

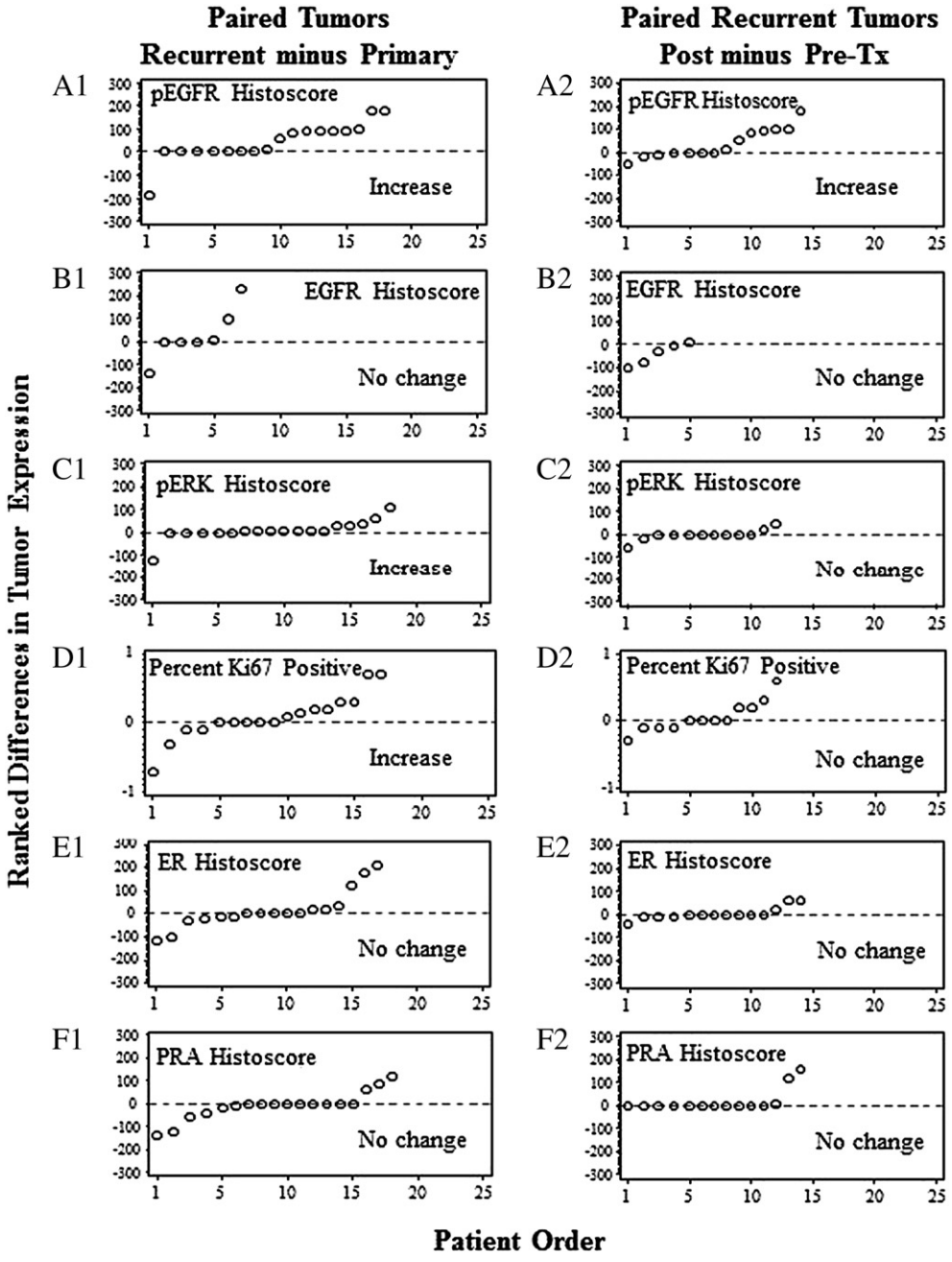

Fig. 3. Ranked difference between pEGFR (A1, A2), EGFR (B1, B2), pERK (C1, C2), Ki67 (D1, D2), ER (E1, E2), or PRA (F1, F2) in recurrent tumors and primary tumors (A1, B1, C1, D1, E1, F1) and in post-treatment and pre-treatment recurrent tumors (A2, B2, C2, D2, E2, F2). ER, PRA, PRB, pEGFR, and pERK were expressed as a histoscore (aggregate of percent of positive tumor cells and staining intensity). Ki67 was expressed as a percent of Ki67 positive tumor cells.

progression. However, treatment with gefitinib did not block EGFR phosphorylation or ERK phosphorylation in all cases. Whether these results can be attributed to suboptimal dosing, primary tumor resistance to gefitinib, or the activation of alternative signaling pathways is not known, and deserves further study. It is important to note that there is an increased risk of obtaining biased results from post-treatment samples due to data missingness, especially if the biomarker is related to treatment efficacy. Five patients progressed before the first scheduled post-treatment sample, so considerable caution needs to be exercised.

The aforementioned tumor markers analyzed by immunohistochemistry also were tested for associations with survival. Previous studies have demonstrated an association (positive or negative) between survival and expression of ER [42–44,48–67], PR [42–44,48,49,51–54,57–64], and Ki67 in primary endometrial carcinoma [65,66]. Our analyses did not find associations between the immuno-detection of these selected biomarkers and patient survival; however, it must be noted that the patient population was specifically selected for progression to an advanced disease stage following chemotherapy, as opposed to an unselected population.

Notably, baseline serum concentrations of sEGFR were associated with OS in this small patient population. Serum concentrations of sEGFR have been reported to vary in post-menopausal within the range of 519–31,465 fmol/ml [68]. In tumors, while the range remains broad, the sEGFR quartile level is prognostic for outcome. In most cancers, including ovarian, lung and colorectal cancer, reduced concentrations of serum sEGFR have been correlated with poor prognosis [15], consistent with the findings in this study where elevated sEGFR predicted positively for OS. Women with high concentrations of serum sEGFR had an estimated 68% reduced risk of death (HR = 0.320; 95% CI: 0.128–0.796). The patient who achieved a CR and three of four patients with PFS ≥6 months had high baseline serum sEGFR concentrations. Since only one of 26 patients

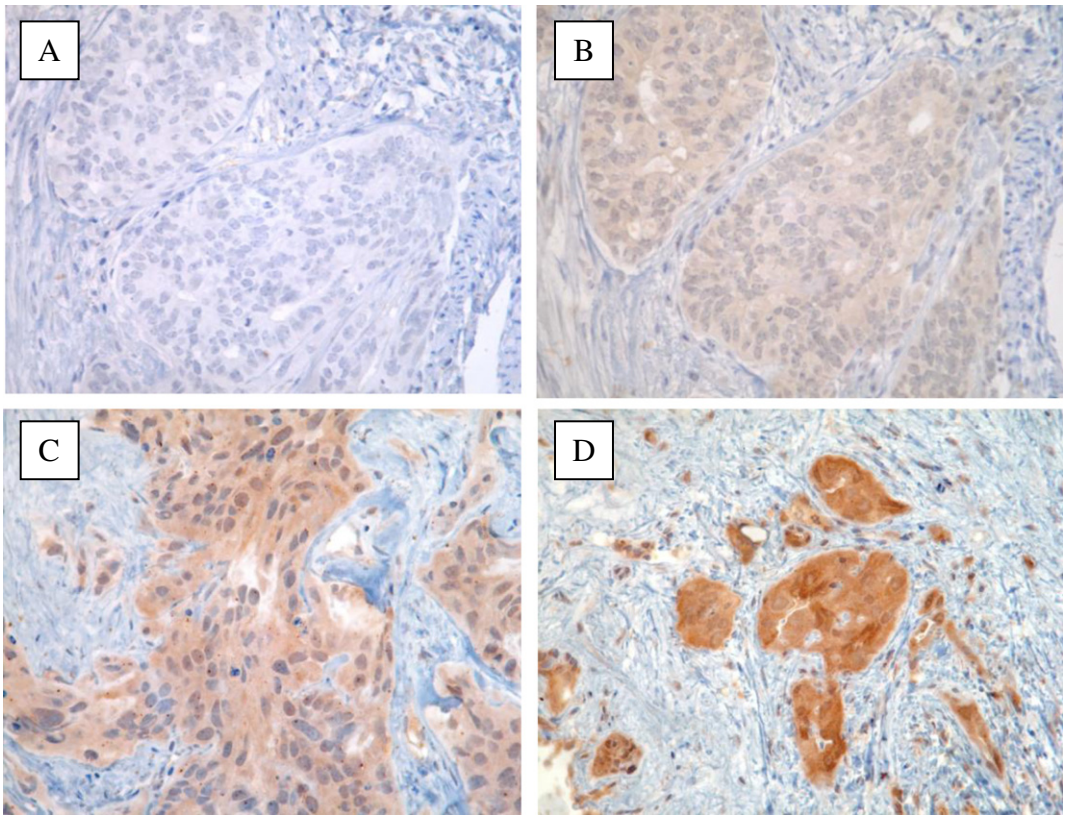

Fig. 4. Expression of pEGFR as determined by IHC in primary and recurrent endometrial tumors. Negative control staining in primary tumor is shown in panel A. pEGFR staining is preferentially localized in primary tumor cells (panel B), pre-treatment recurrent tumor cells (panel C), or post-treatment recurrent tumor cells (panel D).

had a CR to gefitinib treatment, and only seven patients had stable disease, the size of this study was underpowered to observe statistically significant associations between serum sEGFR and CR or PFS. Nevertheless, these results suggest that high vs. low serum sEGFR concentrations may be useful in predicting PFS and OS among patients with persistent or recurrent endometrial cancer.

While the biological basis for the association between serum sEGFR and OS is not yet known, the potential of sEGFR to function as a decoy receptor, thereby regulating ligand bio-availability, as well as its role in cell cohesion and survival signaling may contribute to this phenomenon [69]. Given the paucity of prognostic and theragnostic biomarkers predictive of survival and treatment responsiveness, respectively, in endometrial cancer, these results warrant validation as well as further study regarding the contribution of this novel alternate EGFR isoform to the biology of endometrial cancer. In this regard, sEGFR expression also has been detected in endometrial cancer-derived cell lines [33]. Since our previous studies have shown a correlation between serum sEGFR and gonadotropin concentrations [68], as well as responsiveness to the aromatase inhibitor letrozole [13], future studies examining the interplay between steroid hormones, gonadotropins, and the EGFR/HER receptor growth regulatory axis in endometrial cancer cells may shed further light on the interrelationships among these important endometrial growth regulatory factors.

Although only one patient responded to gefitinib monotherapy, it is interesting that this patient achieved a CR and did not harbor any detectable EGFR mutations that could be associated with sensitivity to gefitinib, such as those observed in NSCLC. Though the preponderance of evidence thus far suggests limited efficacy of EGFR inhibitors for endometrial cancer, this CR demonstrates that some patient subpopulations will respond to gefitinib. A better understanding of the phenotypes of responsive endometrial cancer subpopulations, including the development of methods to identify those patients most likely to respond to gefitinib, will be required for this drug to become a viable treatment option for patients with endometrial cancer.

Conflict of interest

Andre Baron and Nita Maihle are co-inventors on patents related to sEGFR and are co-founders of a biotechnology company that holds the rights to these patents. Of note, these investigators were blinded to all clinical data during the conduct of these studies and were not involved in the statistical analyses or interpretation of the statistical results of these analyses.
All other co-authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2013.02.019.

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