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Phase II Trial of Cetuximab and Carboplatin in Relapsed Platinum-Sensitive Ovarian Cancer and Evaluation of Epidermal Growth Factor Receptor Expression: A Gynecologic Oncology Group Study

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Abstract

Purpose—This phase II trial assessed the activity and tolerability of cetuximab (C225, Erbitux) in combination with carboplatin in patients with relapsed platinum-sensitive ovarian or primary peritoneal carcinoma.

Patients and Methods—Patients were to receive combination therapy with cetuximab (initial dose of 400 mg/m² intravenously on cycle 1, day 1, followed by weekly infusions of 250 mg/m²) and carboplatin (AUC of 6 on day 1 and every 3 weeks). The primary objectives of this trial were to estimate the anti-tumor activity and adverse events of this combination therapy. Immunohistochemical expression of EGFR was evaluated in tumor specimens from patients enrolled in this trial.

Results—Of the 29 patients, 28 (97%) were eligible and evaluable for analysis of the efficacy and toxicity of cetuximab administered in combination with carboplatin. Of the evaluable entries, 26 had EGFR-positive tumors and the response rate in this group of patients was as follows: 9 demonstrated an objective response (3 CR; 6 PR) and 8 had stable disease. The response rate did not meet criteria for opening a second stage of accrual. The median time to progression was 9.4+ months (range: .9–22.2+). The most commonly observed adverse events were dermatologic toxicity (grade 3 in 32%), thrombocytopenia (grade 3 in 14%), and hypersensitivity reactions (grade 3 and 4 in 18%).

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Conclusions—Cetuximab administered in combination with carboplatin had modest activity in screened patients with EGFR-positive, relapsed platinum-sensitive ovarian or primary peritoneal carcinoma. Cetuximab was associated with an acneiform rash in a majority of patients and occasional serious hypersensitivity reactions.

Keywords

cetuximab; epidermal growth factor receptor; ovarian cancer

INTRODUCTION

Cetuximab (C225, Erbitux) is a novel biologic agent that has been shown in both *in vitro* studies and *in vivo* animal xenograft models to have profound synergy when combined with either platinum drugs or with other chemotherapeutic agents or radiation therapy [1,2]. Cetuximab, a chimerized monoclonal antibody, was developed to target the epidermal growth factor receptor (EGFR). EGFR is a 170-kd transmembrane glycoprotein receptor found on cells of epithelial origin [3]. EGFR has important growth regulatory functions which are activated upon ligand binding and EGFR signaling and has been associated with tumor cell growth, angiogenesis, invasion, and metastasis. Cetuximab binds to the extracellular domain of the EGFR thereby preventing ligand activation of EGFR [4]. The resultant inhibition of EGFR signaling can lead to cell cycle arrest, cell death via apoptosis, and inhibition of cell invasion and angiogenesis.

Overexpression of EGFR mRNA and/or protein has been documented in a number of malignancies, including ovarian cancer. Approximately 35% to 70% of ovarian cancers expressed EGFR mRNA analyzed via reverse transcriptase-polymerase chain reaction and radioligand binding assays and 98% demonstrated EGFR protein expression by Western blot analysis [5–7]. High EGFR expression in ovarian cancer specimens has been associated with advanced stage, an aggressive phenotype, and poor clinical outcome [5,6,8,9]. In addition, high EGFR expression has been associated with chemotherapy resistance in human cancer cell lines. EGFR expression as well as the expression of EGFR-related proteins has been shown to become more intense and diffuse in tumor specimens obtained after treatment with cisplatin compared to the staining in matched pretreatment tumor specimens [10]. Therefore, the use of an EGFR inhibitor such as cetuximab to disrupt the EGFR signaling pathway could potentially inhibit the emergence of chemotherapy resistance.

In preclinical studies, cetuximab has been found to repress the growth of cultured A431 tumor cell lines and xenografts that express high levels of EGFR [11,12]. Cetuximab has also been shown to enhance the effects of a variety of chemotherapeutic agents, including platinum compounds, in a variety of human tumor cell lines that express the EGFR, including ovarian cancer cell lines [1,8,13,14]. These intriguing preclinical findings have been supported by the results of clinical trials that revealed that the addition of cetuximab plus cisplatin in patients with platinum-resistant squamous cell carcinoma of the head and neck resulted in objective responses [15]. Furthermore, phase III clinical trials demonstrated that combination cetuximab and chemotherapy yielded superior response rates and in some cases improved survival in patients with head and neck cancer and colorectal cancer [16,17].

Cetuximab has been shown to be well tolerated with predictable pharmacokinetic parameters in phase I trials [18]. In a phase Ib study of cetuximab in combination with cisplatin, the optimal biologic dose was determined to be a loading dose of cetuximab 400 mg/m² and a weekly maintenance dose of 250 mg/m² to achieve tumor EGFR saturation [18]. Combination carboplatin and cetuximab therapy has been studied in two phase II trials, one including gemcitabine and one with paclitaxel in advanced non-small-cell lung cancer (NSCLC) [19,

20]. The most frequent cetuximab-related adverse event in both trials was an acne-like rash (grade 3: 13–20%) [19,20]. The encouraging results of these studies indicate that cetuximab is well tolerated with systemic platinum-based chemotherapy.

The present phase II trial was undertaken to assess the anti-tumor activity and toxicity of cetuximab in combination with carboplatin in patients with recurrent or persistent, platinum-sensitive ovarian carcinoma or primary peritoneal cancer. In addition, the immunohistochemical expression of EGFR was evaluated in archival tumors from the patients enrolled on this trial.

MATERIALS AND METHODS

Eligibility

Eligible patients must have had platinum-sensitive recurrent epithelial ovarian or primary peritoneal carcinoma to enroll on Gynecologic Oncology Group (GOG) protocol 146P. Confirmation of persistent or recurrent disease was required and could be documented either clinically or histologically. Patients must have had one prior platinum-based chemotherapeutic regimen for management of primary disease. This initial treatment may have included consolidation therapy, or extended therapy administered after surgical or non-surgical assessment. Patients who had not received initial therapy with paclitaxel may have received a second regimen that included paclitaxel. Patients who received any prior anti-epidermal growth factor receptor antibody therapy, therapy with a tyrosine kinase inhibitor that targets the EGFR pathway or prior chimerized or murine monoclonal antibody therapy were not eligible.

Patients were required to have measurable disease defined as at least one lesion that can be accurately measured in at least one dimension. Each lesion must be ≥ 20 mm when measured by conventional techniques, including palpation, and imaging studies, or > 10 mm when measured by spiral CT. Additional requirements included a GOG performance status of 0 to 2; adequate bone marrow (absolute neutrophil count $\geq 1,500/\mu\text{L}$, platelet count $\geq 100,000/\mu\text{L}$), renal (serum creatinine ≤ 1.5 times the upper limit of normal), hepatic (total bilirubin ≤ 1.5 times upper limit of normal and transaminases and alkaline phosphatase ≤ 2.5 times upper limit of normal), and neurologic function grade ≤ 1 . Patients must be considered platinum-sensitive according to standard GOG criteria, i.e., a treatment-free interval without clinical evidence of progressive disease following response to platinum of greater than 6 months.

Patients provided written informed consent consistent with federal, state, and local institutional requirements to participate in the clinical and translational research components of this protocol. In addition, the protocol was approved by the institutional review board at each of the participating GOG institutions and done in accordance with assurances filed with and approved by the Department of Health and Human Services. Histologic diagnosis for each patient enrolled on this protocol was confirmed by members of the GOG Pathology Committee.

Treatment plan and dose modifications

Cetuximab (Bristol-Myers-Squibb, New York, New York) was administered at an initial loading dose of was 400 mg/m^2 IV on cycle 1, day 1, followed by weekly infusions of 250 mg/m^2 IV. Carboplatin was administered after cetuximab at an area under the curve (AUC) of 6 mg/ml/min IV on day 1 of each 3 week cycle. The treatment regimen was continued until disease progression or adverse effects prohibited further therapy. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria Version 3.0. Patients who experienced the first occurrence of a grade ≥ 3 rash had therapy held until improvement. Patients who experienced a second and third occurrence were held until improvement and then dose reduced to $200 \text{ mg/m}^2/\text{wk}$ and $150 \text{ mg/m}^2/\text{wk}$, respectively. Those who experienced a fourth occurrence

were removed from the study. Patients who experienced a grade 1 or 2 infusion reaction secondary to cetuximab were administered cetuximab at 50% of the original infusion rate. If the subject had a second infusion reaction with the slower infusion rate, or if they experienced a grade 3 or 4 reaction they were removed from the study. In the case of hypersensitivity reactions to carboplatin, carboplatin desensitization could be performed at the discretion of the investigator. Patients who experienced another reaction despite desensitization were removed from the study. Cetuximab omission for more than four consecutive infusions for toxicity or carboplatin administration delay for more than 2 weeks required removal from protocol treatment.

Response assessment

Patients were to be clinically evaluated every 4 weeks and radiographically every 8 weeks. The same evaluation modality was to be used throughout for each patient on the study. Response criteria were used as defined by Response Evaluation Criteria in Solid Tumors [21]. Patients were deemed inevaluable for response if no repeat tumor assessments following initiation of study therapy for reasons unrelated to symptoms or signs of disease.

Immunohistochemistry assay for epidermal growth factor receptor

Fixed archival tumor tissue specimens either from the primary, secondary or interval surgery were tested for EGFR expression using an EGFR Immunohistochemistry Assay performed by IMPATH (Los Angeles, California) using the Dako EGFR pharmDx™ Kit for Manual Use (#K1492, clone 218C9) (Carpinteria, California). Patients with both EGFR positive and negative cancer specimens were eligible for enrollment onto the trial. Positivity for EGFR expression was defined as any membrane staining above background level, whether or not completely circumferential. Absence of staining was reported as negative. All slides were submitted to the GOG for an independent pathologic review. The GOG reviewer, WHR, was blinded to clinical outcome and response status, and evaluated the slides to assess staining intensity (0, 1+, 2+, or 3+) and % of tumor cells stained. Absence of staining within the tumor was scored as a 0. Positive staining was defined as any staining of the tumor cell membrane and was further characterized as 1+ (low), 2+ (moderate), and 3+ (strong).

Statistical methods

The primary end point used to evaluate drug efficacy was response rate. This study featured two separate subgroups, one for EGFR-positive patients and one for EGFR-negative patients. Each was to be evaluated separately and no comparisons were planned. Prior to entry, the patient's EGFR status was determined and required at the time of registration. Each evaluation implemented an optimal but flexible two-stage design with early stopping guidelines intended to limit the accrual of patients to inactive treatments [22]. Arbitrarily it was determined that if the cetuximab and carboplatin combination had a response rate of 40% or less, it would be of no clinical interest. Conversely, if the true response rate was at least 60%, further study would be clearly indicated. If the true response rate was 40% (H_1), these decision rules limited the average probability of designating the treatment as active to 5%. On the other hand, if the true response rate was 60% (H_2) then the average probability of correctly classifying the treatment as active was 90% [22].

An additional primary objective of this trial was to determine the nature and degree of toxicities associated with cetuximab in combination with carboplatin. The secondary end points used to evaluate drug efficacy included overall survival, progression-free survival (PFS), and duration of response. An exploratory objective was to determine the proportion of patients with advanced ovarian cancer whose tumors overexpressed EGFR.

RESULTS

Patients and eligibility

Of the 29 patients enrolled onto the trial, one patient was not eligible (treatment-free interval <12 months). Patient characteristics are listed in Table 1. Twenty (71%) patients had serous adenocarcinomas, half had grade 3 cancers (14/28; 50%), and all patients had a platinum-free interval of greater than 12 months (median, 19 months; range, 13–98 months). All patients had received only one prior taxane and platinum-based cytotoxic regimen. Three patients were treated with consolidation therapy; two with liposomal doxorubicin and one with interferon.

Treatment responses

Patients received a median of 4 cycles (range, 1–12) of therapy. Of the 28 evaluable entries, 26 (92.9%) had EGFR-positive tumors and only 2 had EGFR-negative tumors. Initially, two separate evaluations were to be performed; one for the EGFR-positive patients and one for the EGFR-negative patients. Given the paucity of patients with EGFR-negative cancers, this component of the investigation was not feasible. Response data is presented for the EGFR-positive patients only (Table 2). The response rate in this group of patients was as follows: 9 (34.6%) demonstrated an objective response (3 (11.5%) CR; 6 (23%) PR) and 8 (30.8%) had stable disease (Table 2). Three (11.5%) patients had progressive disease and 8 (30.8%) were not evaluable for response. The median time to progression was 9.4+ months (range: .9–22.2+). There was not an association between response and rash severity ($p=0.131$) (Table 5).

Toxicity

The most commonly observed toxicities were grade 3 dermatologic toxicity (32%), grade 3 thrombocytopenia (14%), and metabolic toxicity (14%). Hypersensitivity reactions occurred in 9 patients (32%), including 5 (18%) grade 3 and 4 reactions. Three reactions were attributed to cetuximab and four were attributed to carboplatin. In two cases, the reaction could not be definitively attributed to one specific agent. (Table 3)

Twelve (43%) patients only received 1 or 2 cycles of therapy. Three of these patients discontinued protocol treatment due to progressive disease, one refused further therapy, and the remainder discontinued due to toxicity (5 had hypersensitivity reactions, 2 had dermatologic reactions, one had delayed ANC recovery). Of the 5 hypersensitivity reactions requiring discontinuation of therapy, 3 were due to cetuximab and 2 were due to carboplatin.

Baseline expression of epidermal growth factor receptor in ovarian tumor samples

Archival tumor specimens were submitted for all 28 of the enrolled eligible patients who participated in this trial to assess immunohistochemical expression of EGFR. Positive EGFR expression (+1 or greater) was observed in 26 (92.9%), and 2 (7.1%) of the cases were deemed negative (Table 4).

The independent review reported positive EGFR expression in 24 (85.7%) of the tumors examined, and negative expression in 4 (14.3%) of the cases (Table 4)(Figure 1). Thus, there was substantial agreement between the two separate evaluations characterizing EGFR expression ($Kappa = 0.67$)[23]. Among the EGFR-positive tumors, 33.3% (8/24), 29.2% (7/24), and 37.5% (9/24) displayed low EGFR levels (1+), moderate EGFR levels (2+), and high EGFR levels (3+), respectively. Of the cases that displayed low EGFR levels, staining was observed in $\leq 10\%$ of the tumor cells in 75% (6/8) of cases, $>10\%$ in one case, and 25% in one case. Similarly, in cases with moderate EGFR levels staining was observed in $\leq 10\%$ of the tumor cells in 71% (5/7) of cases, 20% in one case, and $>50\%$ in one case. In contrast, cases with high EGFR levels were more likely to have higher percentage of stained tumor cells with

5 demonstrating 25–50% staining, 3 with 80–90% staining, and only one case with <10% staining.

Of interest, both patients with EGFR-negative cancers responded. The response rates for patients with EGFR-positive tumors were 60%, 40%, and 33% for low (1+), moderate (2+), and high (3+) EGFR staining, respectively (Table 5). We were unable to statistically correlate the degree of staining intensity or percentage of tumor cells stained with response due to the small number of patients enrolled in the study.

DISCUSSION

Cetuximab was combined with carboplatin because of persuasive preclinical and clinical evidence indicating that the combination of cetuximab with cytotoxic agents had increased therapeutic efficacy. Our study demonstrated that the combination of cetuximab with carboplatin in patients with platinum-sensitive ovarian and primary peritoneal cancer has only modest activity. Unfortunately, the extent of activity was not sufficient to warrant further evaluation of this novel combination. Studies in other disease types such as head and neck cancer and colorectal cancer have reported much higher response rates and longer survival rates in patients who received cetuximab in combination with chemotherapy compared to those who were treated with single-agent therapies [16,17]. Our results were somewhat disappointing given these reports in other solid tumors, but are consistent with the data reported from another clinical trial evaluating an inhibitory biologic therapy that targets the EGFR pathway in ovarian cancer [10].

Schilder and colleagues reported that gefitinib, a quinazoline derivative that inhibits EGFR tyrosine kinase activity, had minimal activity in unscreened patients with recurrent ovarian and peritoneal carcinoma [10]. However, that study did report that 1 of 11 (9%) patients with EGFR-expressing cancers had an objective response. In contrast to the Schilder study which was performed in an unscreened sample, our study was conducted in a screened population. The response rate in our study was higher than the Schilder study (26.9% versus 9%) in patients with EGFR-positive cancers but that is most likely due to the addition of a cytotoxic agent, carboplatin, to cetuximab. All patients eligible for our study were to be evaluated separately in two groups: EGFR-positive and EGFR-negative. Interestingly, only two patients in our study had cancers that screened negative for EGFR, while the Schilder study reported that 59% (16/27) of patients had cancers that screened negative for EGFR [10]. One explanation for the significantly higher frequency of EGFR-positive expressing tumors in our study could be that patients were prescreened at their respective institutions and only those who screened positive were enrolled on the current study. Alternatively, there could be significant variability between the immunohistochemical techniques used to determine EGFR status as this portion of the study evaluation was performed at different laboratories.

The response rate and median PFS of single-agent carboplatin in patients with recurrent platinum-sensitive ovarian cancer are 30.9% and 5.8 months, respectively [24]. Our data did not demonstrate a promising response or stable disease rate with the addition of cetuximab to carboplatin. The lower than expected response rate may be due to inhibition of carboplatin by cetuximab or inherent tumor biologic characteristics in our pre-selected patient sample. By enrolling principally only patients with EGFR-positive status we were actually selecting a population that has aggressive tumor biology [5]. Prior GOG studies in patients with platinum-sensitive ovarian cancer, the response rates for single-agent cisplatin, carboplatin, and paclitaxel were 24%, 31%, and 36%, respectively [24–26]. However, EGFR-expressing tumors notoriously have been associated with an aggressive cancer phenotype and poor clinical outcome [5,6,8,9]. Patients with EGFR-expressing ovarian cancer may not reflect the traditional patients typically enrolled on clinical trials for patients with platinum-sensitive

disease. Therefore, we may have inadvertently placed our expectations for success too high in this patient population as EGFR-positive tumors have a far worse prognosis compared to EGFR-negative tumors [5].

Interestingly, clinical data suggest that the response to cetuximab may not be limited to tumors that express high levels of EGFR. Prior colorectal studies have shown no difference between response rates and the intensity of EGFR expression based on immunohistochemistry [17]. The response rates were 20.8%, 24.7%, and 22.7% for faint (1+), weak to moderate (2+), and strong (3+) EGFR staining, respectively. Although our analysis is limited by a small number of patients our descriptive findings indicate that EGFR expression is not predictive of response to cetuximab and that high intensity may actually predict for resistance to cetuximab. Burtneff et al. reported that cetuximab was most active in patients with low-to-moderate EGFR tumor expression compared to those with high EGFR expression [16]. The authors hypothesized that cetuximab may have lower activity specifically in patients with high EGFR tumor expression due to the following: (1) the inability of cetuximab at recommended doses to saturate the high number of EGFRs present in high EGFR expressing tumors; and (2) the inability of cetuximab to inhibit the receptor when high receptor density is present due to stochastic interactions or ligand-independent EGFR mechanisms of activation [16].

Overall cetuximab was well tolerated in this study, with the most common adverse events being hypersensitivity and dermatologic reactions. However, these specific adverse events accounted for early withdrawal in 58% (7/12) of patients who received only 1 or 2 cycles of therapy. Hypersensitivity reactions occurred in 9 patients (32%), including 5 (18%) grade 3 and 4 reactions. Most studies evaluating cetuximab in combination with carboplatin-based chemotherapy have reported a 2–3% incidence of hypersensitivity reactions which is dramatically lower than our findings [20,27,28]. In contrast, Thienelt et al reported a similar incidence of hypersensitivity reactions (32%), however, only 3% had grade 3 reactions [19]. Our study in contrast to other studies included patients who had universally received prior therapy with a taxane and platinum agent. In several of the mentioned reported studies patients had either chemo-naïve disease (19,20) or the majority had not previously been treated with a carboplatin-based regimen (27,28). Carboplatin allergy classically develops after at least four cycles of treatment. A study in the pediatric population found that carboplatin allergy was significantly related to the total number of doses but not to cumulative dose of carboplatin (29). Therefore, the increased incidence of hypersensitivity reactions in our study is most likely due to the high frequency of carboplatin pretreatment in our patient population.

In conclusion, cetuximab administered in combination with carboplatin had only modest activity in screened patients with relapsed platinum-sensitive ovarian or primary peritoneal carcinoma. Cetuximab in combination with carboplatin in our patient population was frequently associated with an acneiform rash and occasional serious hypersensitivity reactions.

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References

1. Prewett M, Rockwell P, Rockwell RF, et al. The biologic effects of C225, a chimeric monoclonal antibody to the EGFR, on human prostate carcinoma. *J Immunother* 1996;19:419–27.
2. Waksal HW. Role of an anti-epidermal growth factor receptor in treating cancer. *Cancer & Metastasis Reviews* 1999;18:427–36. [PubMed: 10855786]
3. Thompson DM, Gill GN. The EGF receptor: structure, regulation and potential role in malignancy. *Cancer Surv* 1985;4:767–88. [PubMed: 2824044]
4. Prewett M, Rothman M, Waksal H, Feldman M, Bander NH, Hicklin DJ. Mouse-human chimeric anti-epidermal growth factor receptor antibody C225 inhibits the growth of human renal cell carcinoma xenografts in nude mice. *Clin Cancer Res* 1998;4:2957–66. [PubMed: 9865906]
5. Bartlett JM, Langdon SP, Simpson BJ, et al. The prognostic value of epidermal growth factor receptor mRNA expression in primary ovarian cancer. *Br J Cancer* 1996;73:301–6. [PubMed: 8562334]
6. Fischer-Colbrie J, Witt A, Heinzl H, et al. EGFR and steroid receptors in ovarian carcinoma: comparison with prognostic parameters and outcome of patients. *Anticancer Res* 1997;17:613–9. [PubMed: 9066588]
7. Illekis JV, Connor JP, Prins GS, et al. Expression of epidermal growth factor and androgen receptors in ovarian cancer. *Gynecol Oncol* 1997;66:250–4. [PubMed: 9264571]
8. Ciardiello F, Tortora G. A novel approach in the treatment of cancer: Targeting the epidermal growth factor receptor. *Clin Cancer Res* 2001;7:2958–70. [PubMed: 11595683]
9. Mendelsohn J. Targeting the epidermal growth factor receptor for cancer therapy. *J Clin Oncol* 2002;20:1S–13S. [PubMed: 12235219]
10. Schilder RJ, Sill MW, Chen XW, et al. Phase II study of gefitinib in patients with relapsed or persistent ovarian or primary peritoneal carcinoma and evaluation of epidermal growth factor receptor mutations and immunohistochemical expression: a Gynecologic oncology group study. *Clin Cancer Res* 2005;11:5539–48. [PubMed: 16061871]
11. Goldstein NI, Prewett M, Zuklys K, et al. Biological efficacy of a chimeric antibody to the epidermal growth factor receptor in a human tumor xenograft model. *Clin Cancer Res* 1995;1:1311–18. [PubMed: 9815926]
12. Fan Z, Baselga J, Masui H, Mendelsohn J. Antitumor effect of antiepidermal growth-factor receptor monoclonal-antibodies plus cis-diamminedichloroplatinum on well established A431 cell xenografts. *Cancer Res* 1993;53:4637–42. [PubMed: 8402640]
13. Balin-Gauthier D, Delord JP, Rochaix P, et al. In vivo and in vitro antitumor activity of oxaliplatin in combination with cetuximab in human colorectal tumor cell lines expressing different level of EGFR. *Cancer Chemother Pharmacol* 2006;57:709–18. [PubMed: 16320055]
14. Sung FL, Poon TCW, Hui EP, et al. Antitumor effect and enhancement of cytotoxic drug activity by cetuximab in nasopharyngeal carcinoma cells. *In Vivo* 2005;19:237–45. [PubMed: 15796181]
15. Herbst RS, Arquette M, Shin DM, et al. Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck. *J Clin Oncol* 2005;23:5578–87. [PubMed: 16009949]
16. Burtneess B, Goldwasser MA, Flood W, et al. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: An eastern cooperative oncology group study. *J Clin Oncol* 2005;23:8646–54. [PubMed: 16314626]
17. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *New Engl J Med* 2004;351:337–45. [PubMed: 15269313]
18. Shin DM, Donato NJ, Perez-Soler R, et al. Epidermal growth factor receptor-targeted therapy with C225 and cisplatin in patients with head and neck cancer. *Clin Cancer Res* 2001;7:1204–13. [PubMed: 11350885]
19. Thienelt CD, Bunn PA, Hanna N, et al. Multicenter phase I/II study of cetuximab with paclitaxel and carboplatin in untreated patients with stage IV non-small-cell lung cancer. *J Clin Oncol* 2005;23:8786–93. [PubMed: 16246975]

20. Robert F, Blumenschein G, Herbst RS, et al. Phase I/IIa study of cetuximab with gemcitabine plus carboplatin in patients with chemotherapy-naïve advanced non-small-cell lung cancer. *J Clin Oncol* 2005;23:9089–96. [PubMed: 16301597]
21. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid Tumors. *J Natl Cancer Inst* 2000;92:205–16. [PubMed: 10655437]
22. Chen TT, Ng TH. Optimal flexible designs in phase II clinical trials. *Stat Med* 1998;17:2301–12. [PubMed: 9819829]
23. Landis JR, Koch GG. Measurement of observer agreement for categorical data. *Biometrics* 1977;33:159–74. [PubMed: 843571]
24. Pfisterer J, Vergote I, Du Bois A, Eisenhauer E. Combination therapy with gemcitabine and carboplatin in recurrent ovarian cancer. *Int J Gynecol Cancer* 2005;15:36–41. [PubMed: 15839957]
25. Markman M, Hoskins W. Responses to salvage chemotherapy in ovarian cancer - A critical need for precise definitions of the treated population. *J Clin Oncol* 1992;10:513–14. [PubMed: 1548513]
26. Omura GA, Brady MF, Look KY, et al. Phase III trial of paclitaxel at two dose levels, the higher dose accompanied by filgrastim at two dose levels in platinum-pretreated epithelial ovarian cancer: An intergroup study. *J Clin Oncol* 2003;21:2843–48. [PubMed: 12807937]
27. Baselga J, Trigo JM, Bourhis J, et al. Phase II multicenter study of the antiepidermal growth factor receptor monoclonal antibody cetuximab in combination with platinum-based chemotherapy in patients with platinum-refractory metastatic and/or recurrent squamous cell carcinoma of the head and neck. *J Clin Oncol* 2005;23:5568–77. [PubMed: 16009950]
28. Chan ATC, Hsu MM, Goh BC, et al. Multicenter, phase II study of cetuximab in combination with carboplatin in patients with recurrent or metastatic nasopharyngeal carcinoma. *J Clin Oncol* 2005;23:3568–76. [PubMed: 15809453]
29. Yu DY, Dahl GVH, Shames RS, et al. Weekly dosing of carboplatin increases risk of allergy in children. *J Pediatr Hematol Oncol* 2001;23:349–52. [PubMed: 11563768]

Figure 1. Immunohistochemical evaluation of EGFR expression in primary epithelial ovarian cancer specimens. High (3+) EGFR expression is present in cancer specimen #23, whereas negative EGFR expression is noted in cancer specimen #14.

Table 1

Patient Demographics (n=28)

	Number
Eligible	28
Age at entry, years	
40–49	4
50–59	8
60–69	9
≥ 70	7
Performance Status	
0	21
1	6
2	1
Race	
White	27
Asian	1
Cell Type	
Serous adenocarcinoma	20
Endometrioid adenocarcinoma	3
Clear cell adenocarcinoma	2
Adenocarcinoma, unspecified	2
Mixed epithelial	1
Grade	
1	2
2	11
3	14
Unspecified	1
Disease Site	
Ovarian	25
Peritoneal	3
Prior Chemotherapy	28
Prior Radiotherapy	0

Table 2Response Rates (n=26)¹

Response Category	Number	%
Complete response	3	11.5
Partial response	6	23.0
Stable disease	8	30.8
Progressive disease	3	11.5
Not evaluable	6	23.0

¹ Analysis limited to patients with EGFR-positive cancers.

Table 3

Adverse Events (n=28)

Adverse Event	Grade		
	2	3	4
Leukopenia	4	2	0
Thrombocytopenia	2	4	0
Neutropenia	7	3	0
Anemia	5	0	0
Alopecia	1	-	-
Dermatologic ^I	9	9	0
Acneiform rash	8	7	0
Gastrointestinal	8	1	0
Nausea/vomiting	3	0	0
SGOT	0	1	0
Neurotoxicity	3	1	0
Pulmonary	6	0	1
Cardiovascular	2	0	0
Allergy	2	4	1
Constitutional	5	2	0
Metabolic	1	3	1
Pain	3	1	0
Infection	3	0	0
Ocular	2	0	0
Hepatic	1	0	0
Fatigue	0	1	0
Endocrine	1	0	0
Auditory	1	0	0
Musculoskeletal	1	0	0
Sexual	1	0	0

^I Dermatologic includes other dermatologic toxicities as well as an acneiform rash.

No treatment-related deaths have been reported.

Table 4
Epidermal Growth Factor Receptor Expression (n=28)^I

Staining intensity	<u>Initial Review</u>		<u>GOG Review</u>	
	Total	%	Total	%
Negative (0)	2/28	7.1	4/28	14.3
Positive	26/28	92.9	24/28	85.7
Low (1)			8/24	33.3
Moderate (2)			7/24	29.2
Strong (3)			9/24	37.5

^I Analysis includes all eligible patients enrolled.

Table 5
Epidermal Growth Factor Receptor Expression and Rash Versus Response (n=20)
¹

Variable	Response (CR + PR)	Clinical Response	
		Stable	Progression
EGFR Staining Intensity			
Negative	2	0	0
Low (1)	3	1	1
Moderate (2)	2	2	1
Strong (3)	2	5	1
Percentage of EGFR-expressing cells			
≤ 10%	3	2	2
>10%	6	6	1
Acne-like rash			
None vs. any			
None	0	1	0
Any	9	7	3
None or grade 1 vs. grade 2 or 3			
None or grade 1	2	4	2
Grade 2 or 3	7	4	1

¹ Analysis includes only patients who were evaluable for response.