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Erlotinib added to carboplatin and paclitaxel as first-line treatment of ovarian cancer: a phase II study based on surgical reassessment

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Abstract

Background—The purpose of this study was to determine whether adding the anti-epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor erlotinib to carboplatin/paclitaxel improved pathologic complete response (pCR) at reassessment surgery in epithelial ovarian, fallopian tube, or primary peritoneal cancers (OFPC).

Methods—Patients with stage III-IV OFPC initiated treatment within 12 weeks of initial cytoreductive surgery or, after histologic confirmation of diagnosis, neoadjuvantly. Treatment included paclitaxel (175 mg/m^2) and carboplatin (AUC 6) every 3 weeks for up to 6 cycles, plus oral erlotinib 150 mg daily. The primary objective was to determine whether the pCR rate at reassessment surgery was at least 60% after optimal cytoreduction at initial surgery (< 1 cm residual disease), or at least 40% after suboptimal cytoreduction (at least 1 cm residual disease) using a two-stage design (alpha = 0.10, beta =0.10).

Results—The study population included 56 patients with stage III-IV OFPC. EGFR gene amplification was present in 15% of the 20 tumors evaluated. Twenty-eight patients had protocol therapy after optimal cytoreduction (stratum I), 23 had protocol therapy either after suboptimal cytoreduction (stratum II), and 5 received neoadjuvant therapy prior to cytoreduction (stratum III).

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Pathologic CR was confirmed in 8 patients (29%; 95% confidence intervals 13%, 49%) in stratum I and 3 patients (11%, 95% C.I. 2%, 28%) in stratum II, which did not meet the prespecified efficacy endpoint in either stratum.

Conclusions—Among unselected patients, erlotinib plus carboplatin-paclitaxel is not more effective than historical experience with carboplatin-paclitaxel alone in patients with stage III-IV OFPC.

Introduction

Epithelial ovarian cancer accounts for approximately 5% of all cancer deaths in women, and is the most common cause of death among the gynecologic malignancies in North America, Western Europe, and Scandinavia.[1, 2] More than 75% patients with epithelial ovarian cancer present with advanced stage disease at presentation.[3] Despite improvements in survival using a combination of platinum and paclitaxel-based chemotherapeutic regimens,[4] only about 30% of patients with advanced stage ovarian carcinoma survive 5 years, and only about 10% are long term survivors.[3] Recent evidence suggests new cytotoxic regimens are not more effective than the standard regimen of carboplatin and paclitaxel.[5] New therapeutic strategies are needed.

The epidermal growth factor receptor (EGFR) pathway is a potential therapeutic target in epithelial ovarian cancer and other gynecological cancers arising from coelomic epithelium, including epithelial cancers of the fallopian tube and peritoneal cavity. EGFR protein expression is observed in about 30% of epithelial ovarian cancer, and EGFR gene amplification is present in about 20%.[6] High tumor EGFR expression has been associated with poor disease free and overall survival after debulking surgery and platinum based chemotherapy.[7] Therapeutic agents targeting EGFR include antibodies (cetuximab, panitumumab[89]) and small molecule tyrosine kinase inhibitors (gefitinib, erlotinib[10, 11]). Some evidence suggests that chemotherapy resistant disease may be more sensitive to EGFR-directed therapies, and that EGFR-directed therapies may exhibit complementary antitumor effects to standard cytotoxic therapy. For example, the paclitaxel resistant A2780 ovarian cancer cell line has been shown to exhibit enhanced sensitivity to the inhibitory effects of erlotinib.[12] In addition, treatment with an EGFR inhibitor in the Caov3 ovarian cancer cell line enhanced paclitaxel-induced cell death in vitro.[13]

Based upon these considerations, we initiated a phase II trial of the EGFR tyrosine kinase inhibitor erlotinib in combination with standard carboplatin-paclitaxel chemotherapy in patients with advanced epithelial ovarian, fallopian tube, and peritoneal cancer (OFPC) after initial cytoreductive surgery. The primary endpoint was pathologic complete response observed at reassessment laparotomy in the study population compared with that expected for a similar population treated with standard chemotherapy alone. Pathologic CR at reassessment surgery after protocol therapy was selected as the primary study endpoint because it is a short term surrogate endpoint known to be associated with improved survival.[14] A secondary objective was to determine the prevalence of EFGR gene amplification in this population as a biomarker that may predictive of benefit from this therapeutic approach.

Methods

Eligibility Criteria

Eligibility criteria including histologically-documented International Federation of Gynecologist and Oncologist (FIGO) stage III-IV epithelial ovarian, primary peritoneal or fallopian tube cancer with no prior chemotherapy for treatment of the disease. Patients were

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required to have had an appropriate debulking surgical procedure by a gynecologic oncologist within 12 weeks of registration. Patients who were deemed by a gynecologist oncologist to be not eligible for primary debulking surgery were also eligible if histologic confirmation of diagnosis was obtained. Other eligibility criteria included: (1) Gynecologic Oncology Group (GOG) performance status 0, 1, or 2, (2) adequate bone marrow (absolute neutrophil count ≥ 1500/uL, platelet count ≥ 100,000/uL), hepatic (transaminases ≤ 2.5-fold above the upper limit of normal, total bilirubin ≤ 1.5-fold above the upper limit of normal) and renal (serum creatinine ≤ 1.5-fold the upper limit of normal) function, (3) no neuropathy, (4) no medical contraindications to the planned regimen, including ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements, (5) no other malignancy within five years of study enrollment, (6) no treatment with other investigational agents, (7) no known brain metastases, (8) no history of allergic reaction attributed to agents of similar biologic or chemical composition as those used in the study, (9) not known to be pregnant or lactating, or (9) not known to be infected with the human immunodeficiency virus.

Informed consent and regulatory approval

The study was reviewed and approved by the Cancer Evaluation Therapy Program of the National Cancer Institute (P5886), and by the institutional review board (IRB) at each participating institution (Clinical Trials.gov identifier NCT00059787). All patients provided written informed consent reviewed and approved by the local IRB at each participating site.

Treatment plan

All patients received paclitaxel and carboplatin administered intravenously on day 1 of each 21-day cycle for a total of six cycles. The initial paclitaxel dose was 175 mg/m2 (maximum paclitaxel dose per cycle was 350 mg). Carboplatin was dosed according to the Calvert formula, at an area under the curve (AUC) of 6, with the calculated creatinine clearance (utilizing the Jellife method) estimating glomerular filtration rate (GFR).[15] Carboplatin/paclitaxel cycles were repeated every 21 days if the absolute neutrophil count was 1500/uL, platelets at least 100,000/uL, and there was satisfactory recovery from toxicity associated with previous treatment cycles. The treatment plan also included erlotinib, 150 mg PO daily on a continuous basis beginning with day 1 of the first carboplatin-paclitaxel cycle. Erlotinib compliance was monitored by pill counts at each visit for chemotherapy. Chemotherapy treatment was discontinued prior to six cycles if there was disease progression, intercurrent illness which prevented further treatment, unacceptable adverse events which precluded continued treatment, patient refusal to continue, or a change in the patient's condition which rendered continued treatment unacceptable to the patient or treating physician. Clinicians were permitted to obtain CA-125 levels, but treatment was given according the guidelines outlined above.

Erlotinib was held in patients who developed grade 3 or greater rash or diarrhea (or grade 2 rash or diarrhea poorly tolerated by the patient). Erlotinib was resumed after the toxicity improved to grade 0-1, with the erlotinib dose decreased to 100 mg daily for a first dose reduction, and 50 mg daily for a second dose reduction. Patients with unresolved toxicity after 2 weeks or requiring a delay in erlotinib dosing for 3 weeks or more were removed from study. After completion of carboplatin-paclitaxel plus erlotinib therapy, patients were eligible to receive erlotinib maintenance therapy (150 mg PO daily for up to 12 months). Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v 3.0 (CTCAE). Erlotinib (Tarceva®, OSI Pharmaceuticals, Melville, NY) was supplied by the Division of Cancer Treatment and Diagnosis (DCTD) of

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the National Cancer Institute (NCI) under a Clinical Trials Agreement between OSI Pharmaceuticals Inc. and the DCTD, NCI.

Evaluation of EGFR Gene Amplicificaiton

DNA was purified from 15-33 mg of frozen tumor tissue using steps detailed in and materials provided in a Qiagen puregene tissue kit. For each sample, a total of 2.2 μg of ssDNA, labeled and fragmented with the NuGEN kit, was hybridized to Affymetrix arrays (Human U133 plus 2.0), following the manufacturer's instructions as described previously.[16] After washing and staining with biotinylated antibody and streptavidin phycoerythrin, the arrays were scanned with the Affymetrix GeneChip Scanner 3000 for data acquisition. The degree of expression of EGFR was determined by a comparison with a pool of DNA samples processed in the same manner as above.

Response assessment

Surgical reassessment was performed by either laparoscopy or laparotomy to determine whether pathologic complete response (pCR) was achieved within eight weeks of completion of chemotherapy. pCR was defined as having no pathologic or cytologic evidence of disease following surgical reassessment. [14]

Maintenance therapy after surgery

Following surgical reassessment, patients with pCR resumed erlotinib (150 mg daily) for up to 12 months. Additionally, patients from any stratum exhibiting complete clinical response but declining surgical reassessment, or patients from stratum 2 or 3 exhibiting response, even if less than pCR, had the option of continuing erlotinib monotherapy. Erlotinib was discontinued prior to 12 months if there was disease progression, unacceptable toxicity, and the patient declined further therapy.

Statistical considerations

The primary study endpoint was pCR determined at the time of reassessment surgery after completion of 6 cycles of carboplatin-paclitaxel plus erlotinib. pCR was evaluated separately in patients with optimally debulked disease (stratum I) and non-optimally debulked disease (stratum II) at initial surgery. Given the additional toxicity expected for the addition of erlotinib, we believed that we need to define a benchmark that would clearly be indicative of significant activity for the combination. In previous studies, the pCR rate at second look laparotomy after platinum-paclitaxel therapy was approximately 20% in patients with suboptimally debulked disease, and would be expected to be higher in patients who had prior optimal debulking. [17, 18] For stratum I, the trial was designed to distinguish between a pCR rate of 40% versus 60%.. For stratum II, the trial was designed to distinguish between a pCR rate of 20% versus 40%. .. Both strata employed Simon's minimax two-stage design (alpha = 0.10, beta =0.10). In stratum I, accrual would proceed to the second stage if at least 12 of 28 evaluable subjects had a pCR; the regimen would be considered promising if at least 21 of 41 eligible/evaluable subjects had a pCR. In stratum II, accrual would proceed to the second stage if at least 4 of 19 evaluable subjects had a pCR; the regimen would be considered promising if at least 11 of 36 evaluable subjects had a pCR. The analysis plan for stratum III was to provide descriptive results regarding the efficacy and safety of the regimen, and no formal statistical objectives were established.

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Results

Patient characteristics

Fifty six patients were enrolled between June 2003 and December 2006. The characteristics of 56 enrolled patients are shown in Table 1**,** including 28 patients enrolled after optimal debulking surgery (stratum I), 23 patients who enrolled after suboptimal debulking surgery (stratum II), and 5 patients with stage IV disease and who were deemed not to be appropriate candidates for cytoreductive surgery (stratum III).

Administration of erlotinib plus carboplatin/paclitaxel

Of the 56 patients enrolled, 36 (64%) completed six cycles of the erlotinib-chemotherapy combination, and 20 (36%) did not. Reasons for discontinuing protocol therapy prior to completing six cycles included adverse events in 13 patients (23%), disease progression in 2 patients (4%), protocol ineligibility in 1 patient (2%), and other medical problems not associated with treatment in 4 patients (7%), including postoperative infection (N=2), liver disease (N=1), and cardiac disease (N=1).

Administration of maintenance erlotinib alone

Sixteen patients (29%) received maintenance erlotinib therapy for a maximum of one year, including 11 patients with surgically confirmed pCR, 3 patients with less than a pCR at surgery, and 2 patients with clinical complete response who did not undergo reassessment surgery. Twelve of 16 patients (75%) completed one year of maintenance therapy without recurrence, and 4 patients (25%) recurred during maintenance therapy. No patients discontinued maintenance therapy due to adverse events.

Adverse events

Adverse events are summarized in Table 2**.** The most common grade 3-4 adverse events occurring in at least 5% of patients included neutropenia (18%), skin rash (17%), thrombocytopenia (7%), infection (7%), and fatigue (5%). Erlotinib-associated toxicities including skin rash occurred in 46% of patients (including 21% grade 2, 13% grade 3, 4% grade 4), and diarrhea occurred in 25% (including 7% grade 2 and 4% grade 3).

The combination of erlotinib plus carboplatin-paclitaxel was discontinued due to adverse events prior to completing 6 cycles of therapy in 13 patients (23%), including erlotinib-associated toxicities in 9 patients (16%). Erlotinib-associated toxicities which contributed to treatment discontinuation included skin rash in 7 patients (13%), nausea in 1 patient (2%), and hypersensitivity in 1 patient (2%). Other adverse events not attributed to erlotinib contributed to discontinuation of therapy in 4 patients (7%), including hypersensitivity to paclitaxel in 1 patient (2%).

Response evaluation after chemotherapy plus erlotinib

Response data are shown in Table 3. In stratum I, 18 of 28 patients (64%) underwent reassessment surgery. No patient had progressive disease during therapy. Eight of 28 patients achieved pCR (29%, 95% confidence intervals [C.I.] 13%, 49%), 10 patients (36%) had residual disease at reassessment surgery, and 10 patients (36%) did not undergo reassessment surgery for a variety of reasons. Two of 10 patients who did not have reassessment surgery had a complete clinical response but declined surgery and remain without evidence of disease two years after completing erlotinib maintenance therapy (three years following completion of paclitaxel, carboplatin and erlotinib).

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In stratum II, 21 of 23 patients (75%) underwent reassessment surgery. Three of 23 achieved pCR patients (13%, 95% C.I. 3%, 36%), 18 patients (78%) had residual disease at surgery, and 2 patients (9%) did not undergo surgery.

Of the 5 who received neoadjuvant therapy in stratum III, no patient underwent initial cytoreductive surgery. Three patients achieved complete clinical response, one patient had stable disease, and one patient did not complete treatment due to medical comorbidities. At surgery following treatment, four neoadjuvant patients were able to be optimally cytoreduced.

EGFR gene amplification and response to therapy

Tumor specimens were evaluated for EGFR gene amplification by in 20 patients. No amplification was observed in 11 patients (55%), low level amplification in 6 patients (30%), and moderate-high amplification was observed in 3 patients (15%). There was no significant difference in the likelihood of having a pCR for patients with no amplification (2 of 11) compared with those who had some amplification (4 of 9) (p=0.33, Fisher's exact test).

Progression-free survival and overall survival

The product-limit method of Kaplan and Meier was used to estimate progression free survival (Figure 1a) and overall survival (Figure 1b**)** in the 51 patients included in stratum I and II. There were 24 patients who had disease progression and 20 patients who died at the time of the analysis. The 3-year progression-free survival (PFS) rate was 49.2% (95% C.I. 32.6%, 63.9%), and median PFS was 34.3 months (95% C.I. 23.9 - 51.8 months). The 3-year overall survival (OS) rate was 68.2% (95% C.I. 53.5%, 79.2%), and median OS l had not yet been reached. Information by stratum is provided for PFS (Figure 2a) and OS (Figure 2b). For PFS, the 3-year PFS rate was 54.2% (95% CI 32.7%, 71.4%) and median PFS was 50.5 months (95% CI 22.8 months, upper limit not estimated) in the optimal stratum; in the suboptimal stratum, the 3-year PFS rate was 41.0% (95% CI 15.5%, 65.3%) and median PFS was 34.3 months (95% CI 20.7 months, upper limit not estimated). For OS, the 3-year OS rate was 81.5% (95% CI 61.1%, 91.8%) and median OS has not been reached in the optimal stratum; in the suboptimal stratum, the 3-year OS rate was 53.6% (95% CI 32.0%, 71.1%), and the median OS was 53.5 months. (95% CI 13.6 months, upper limit not estimated).

Discussion

We performed a phase II trial of the oral EGFR tyrosine kinase inhibitor erlotinib in combination with first-line carboplatin-paclitaxel chemotherapy in patients with stage III-IV epithelial ovarian, fallopian tube, and peritoneal cancer who had undergone prior cytoreductive surgery, of whom about 80% had a ovarian primary cancer. Our objective was to increase by two-fold the pCR rate at reassessment surgery in those who had gross residual disease at initial cytoreductive surgery (from 20% expected with historical data to 40%), and by 50% in those has had been optimally debulked at initial cytoreductive surgery (from 40% expected with historical data to 60%). We found no evidence that addition of erlotinib to carboplatin-paclitaxel improved the likelihood of achieving a pCR in either population, and conclude that this approach should not be further pursued among unselected patients.

A secondary objective of the study was to evaluate the incidence of EGFR gene amplification. We found moderate-high amplification in 15%, low level amplification in 30%, and no amplification in 55% of the 20 specimens evaluated. Our findings are consistent with another report which included 398 cases of serous ovarian carcinoma, in

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which EGFR gene amplification was detected in detected in 12% and low-level gain in 43%.[19] Low level or greater EGFR amplification was not associated with a higher response rate in our trial, suggesting that enrichment for tumors exhibiting EGFR amplification would not likely identify subjects likely to benefit from erlotinib plus chemotherapy.

Some evidence suggests anti-EGFR directed therapies produce clinical benefit in selected patients with chemotherapy resistant ovarian cancer. For example, a phase II study of cetuximab (400 mg/m2 IV loading dose, then 250 mg/m2 weekly) in 25 patients with refractory ovarian cancer unselected for EGFR tumor overexpression revealed objective response in 1 patient (4%) and stable disease for at least 8 weeks in 9 patients (36%).[20] A phase II trial of gefitinib (500 mg daily) in 27 evaluable patients with refractory ovarian cancer not selected for tumor EGFR overexpression revealed one patient who had an objective response (4%) and four patients who were progression free for at least 6 months (15%); the only responding patient had a mutation in the EGFR catalytic domain.[21] Finally, a phase II study of erlotinib (150 mg daily) in 32 patients with refractory ovarian cancer selected for EGFR tumor overexpression revealed objective response in 2 patients (6%) and stable disease for at least 8 weeks in 15 patients (44%); the development of rash was associated with improved survival.[22] Other studies have likewise reported an association between drug-induced rash and improved outcomes in other cancers treated with EGFR inhibitors, including cetuximab for colorectal cancer[23] and erlotinib for non-small cell lung cancer.[24, 25] Although these studies suggest that selected patients may benefit from erlotinib monotherapy, our study found no evidence for improved outcomes when erlotinib was combined with chemotherapy. These finding are consistent with the activity of erlotinib in non-small cell lung cancer, in which erlotinib has been shown to be associated with improved survival when used as monotherapy[26, 27], but is not associated with clinical benefit when added to cytotoxic therapy.[28,29]

In conclusion, we found no evidence that erlotinib produces clinical benefit when added to standard chemotherapy after initial debulking surgery in patients with ovarian, fallopian tube, or peritoneal cancer. A phase III trial is being conducted by the European Organization of Research and Treatment (EORTC) to evaluate the role of maintenance erlotinib after first line chemotherapy in this population (NCT00263822). This trial will define if there is a role for erlotinib in the management of advanced ovarian cancer.

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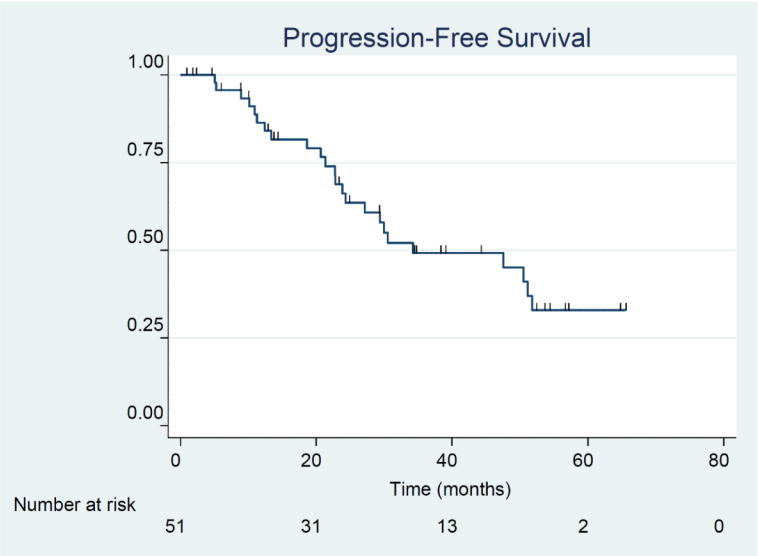

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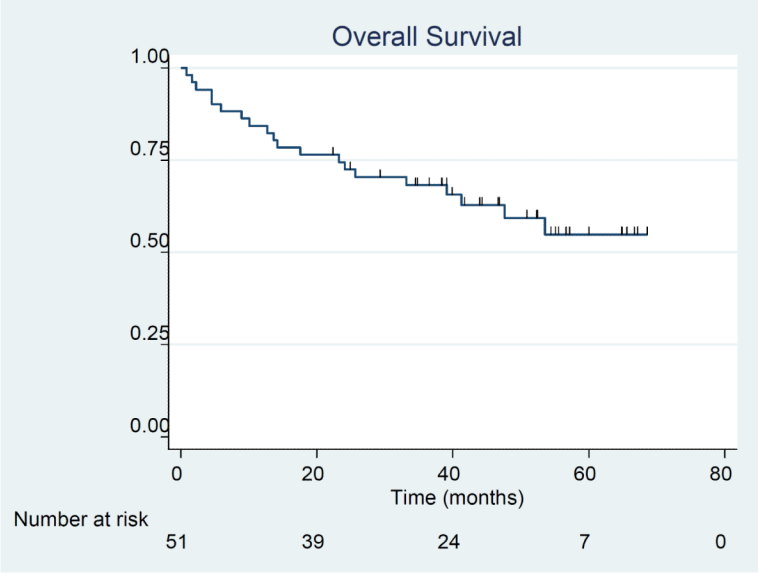

Figure 1a-b.

Progression-free survival (1a) and overall survival (1b) in 51 patients treated with erlotinib plus carboplatin/paclitaxel prior to surgery.

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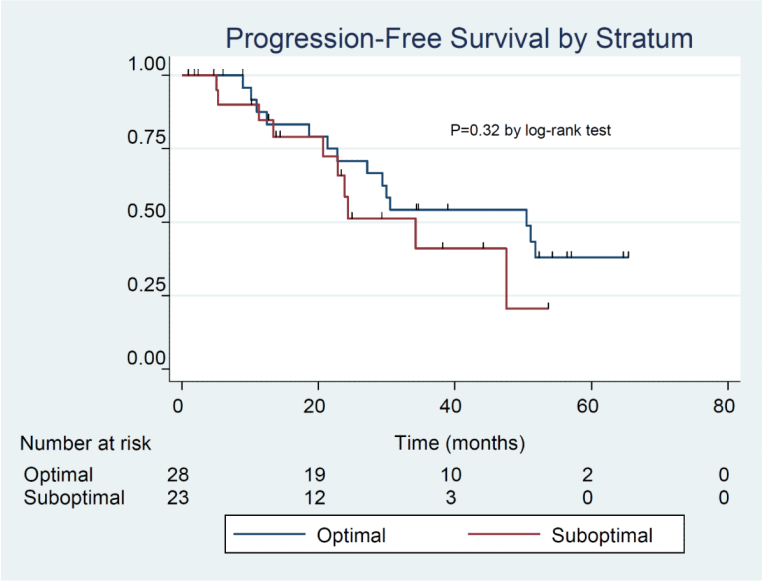
a



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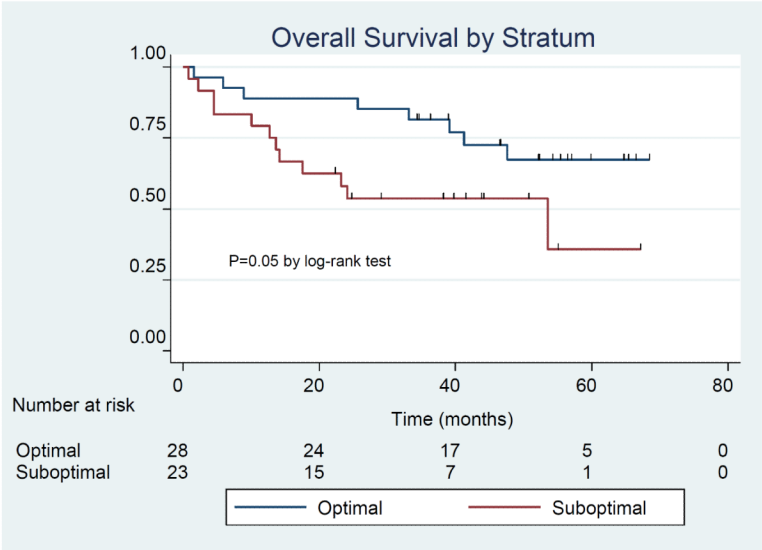

Figure 2a-b.

Progression-free survival (2a) and overall survival (2b) in 51 patients treated with erlotinib plus carboplatin/paclitaxel prior to surgery by treatment stratum.

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Table 1

Patient characteristics

	All patients	Stratum I Optimally Debulked	Stratum II Suboptimally Debulked	Stratum III Neoadjuvant
Total	56	28	23	5
Age (years)				
Median	55.5	57.5	55	53
Range	22-79	23-78	30-75	45-78
Premenopausal	17 (30%)	8 (29%)	7 (30%)	2 (40%)
Ethnicity				
Hispanic	5 (9%)	2 (7%)	2 (9%)	1 (20%)
Non-Hispanic	51 (91%)	26 (93%)	21 (91%)	4 (80%)
Race				
Black	2 (4%)	0 (0%)	1 (4%)	1 (20%)
Asian	5 (9%)	2 (7%)	3 (13%)	0 (0%)
White	42 (75%)	22 (79%)	17 (74%)	3 (60%)
Ashkenazi Jewish	13 (23%)	8 (29%)	3 (13%)	2 (40%)
Smoking history	18 (32%)	11 (39%)	6 (26%)	1 (20%)
Primary Tumor				
Ovary	45 (80%)	22 (79%)	18 (78%)	3 (60%)
Fallopian Tube	3 (5%)	2 (7%)	1 (4%)	0 (0%)
Primary Peritoneal	8 (14%)	4 (14%)	2 (9%)	2 (40%)
Histology				
Papillary serous	37 (66%)	22 (79%)	13 (57%)	2 (40%)
Papillary serous + other	2 (4%)	2 (7%)	0 (0%)	0 (0%)
Other	13 (23%)	3 (11%)	7 (30%)	3 (60%)
Stage				
III	37 (66%)	28 (100%)	9 (39%)	0 (0%)
IV	14 (25%)	0 (0%)	9 (39%)	5 (100%)

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Table 2

Adverse events

	Grades 1-4		Grade 2		Grade 3		Grade 4	—
Toxicity	**No. of Patients**	**%**	**No. of Patients**	**%**	**No. of Patients**	**%**	**No. of Patients**	**%**
Hematologic & Infectious								
Hemoglobin (anemia)	11	20	6	11	2	4	0	0
Neutropenia	14	25	3	5	8	14	2	4
Thrombocytopenia	13	23	4	7	3	5	1	2
Infection	5	4	0	0	3	5	1	2
Non-Hematologic								
Constitutional								
Anorexia	6	11	2	4	0	0	0	0
Fatigue	16	29	5	9	3	5	0	0
Hepatic								
Alkaline phosphatase								
Alanine transaminase (ALT/SGPT)	2	4	0	0	0	0	1	2
Aspartate transaminase (AST/SGOT)	3	8	0	0	0	0	1	2
Mucoenterocutaneous								
Constipation	11	20	3	8	1	2	0	0
Diarrhea	14	25	4	7	2	4	0	0
Mucositis: Oral	6	11	3	8	0	0	0	0
Nausea	11	20	5	9	1	2	0	0
Rash: desquamation	26	46	12	21	7	13	2	4
Vomiting	7	13	5	9	0	0	1	2
Neurologic								
Neuropathy: Sensory	12	21	4	7	0	0	0	0
Pain								
Pain: Abdomen	6	11	2	4	1	2	0	0
Renal/Metabolic								

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	Grades 1-4		Grade 2		Grade 3		Grade 4	—
Toxicity	**No. of Patients**	**%**	**No. of Patients**	**%**	**No. of Patients**	**%**	**No. of Patients**	**%**
Hypokalemia	2	4	0	0	1	2	0	0
Hyperglycemia	2	4	1	2	1	2	0	0

Note: includes all adverse events occurring in at least 5% or where there is at least one occurrence of a grade 3 or 4 event

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Table 3

Results of second look laparotomy

	Stratum I Optimally Debulked	Stratum II Suboptimally Debulked
No.	28	23
No Residual Disease as Surgery	8 (29%) (95% CI 13%, 48%)	3 (13%) (95% CI 3%, 36%)
Residual Disease at Surgery	10 (36%)	18 (64%)
Surgery Not Performed	10 (36%)	2 (9%)
Clinical CR, decline surgery	2	0
Toxicity or other reasons	8	2