

Epidermal growth factor receptor: will it ever become a therapeutic target in ovarian cancer?

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Abstract: Targeted therapies are increasingly being explored in the treatment of ovarian cancer. The epidermal growth factor receptor (EGFR) has received much attention as this pathway is overexpressed and/or amplified in ovarian cancer. Anti-EGFR tyrosine kinase inhibitors (TKIs) and monoclonal antibodies have been studied in combination with chemotherapy and as single agents in both the first-line and relapsed settings but unfortunately, the results have been disappointing. In this editorial, we review a recently published large randomized phase III trial conducted by Vergote *et al.* evaluating maintenance erlotinib in patients with ovarian, peritoneal, or fallopian tube cancer who experienced a response or stable disease (SD) after primary therapy. This study did not show a benefit to maintenance erlotinib and moreover, was not able to identify any subgroups that benefited from erlotinib. Testing for EGFR overexpression and/or amplification by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH), respectively, and mutation testing were performed on archival tumor tissue. Patients who were EGFR positive did have a worse progression-free survival (PFS) and overall survival (OS) but EGFR positivity or the presence of a mutation was not predictive of erlotinib efficacy. At this time, EGFR inhibition in ovarian cancer has not been successful and further targeting of this pathway requires an understanding of resistance mechanisms and the role of other pathways that interplay with EGFR.

Keywords: Epidermal growth factor receptor (EGFR); erlotinib; ovarian cancer; targeted therapies

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Targeted therapies are still seeking a therapeutic role in epithelial ovarian cancer. Poly ADP-ribose polymerase (PARP) inhibitors, agents that target the function of the PARP family of enzymes involved in DNA repair, and bevacizumab, a monoclonal antibody that binds vascular endothelial growth factor A (VEGF-A) represent exceptions: they have shown activity and are being incorporated into current regimens in gynecologic malignancies (1). In contrast, the epidermal growth factor receptor (EGFR) a 170-kd transmembrane glycoprotein receptor, has been extensively studied but its validity as a target beyond non-small cell lung cancer (NSCLC) where EGFR tyrosine kinase inhibitors (TKIs) have been shown to significantly prolong progression-free survival (PFS) in patients who carry an EGFR activating mutation has yet to emerge (2). Nevertheless, the *EGFR* gene, located on chromosome 7p12, is amplified in approximately 4% to 22% of ovarian cancers

and the pathway is overexpressed in 55% to 98% of advanced epithelial ovarian carcinomas (3,4). Overexpression of EGFR is associated with a worse prognosis (4).

Studies with EGFR TKIs

Multiple studies have evaluated EGFR TKIs in ovarian carcinomas. Hirte *et al.* enrolled 50 patients, stratified by platinum sensitivity (n=33 in platinum-sensitive arm and n=17 in platinum-resistant arm), and treated with erlotinib 150 mg daily and carboplatin at an AUC of 5 every 21 days. The objective response rate (ORR) was 57% in the platinum-sensitive arm and 7% in the platinum-resistant arm; 71% of archival tumors stained positive for EGFR. In platinum-sensitive patients with EGFR-positive tumors, there were 12 responses (60% ORR) and the responding platinum-resistant patient was also EGFR-positive. While

well-tolerated, the addition of erlotinib was disappointing in reversing platinum-resistance (5). Blank *et al.* conducted a phase II study of erlotinib added to carboplatin and paclitaxel in first-line treatment. The primary endpoint, pathologic complete response (pCR) at surgical reassessment, was evaluated separately in optimally debulked and non-optimally debulked disease at initial surgery. A proportion of 36/56 (64%) patients completed six cycles of the erlotinib-chemotherapy combination. The primary objective, increasing pCR by two-fold compared to historical data, was not met: pCRs were 29% and 13% in the optimally and suboptimally debulked groups, respectively. EGFR gene amplification was not associated with response rate (6).

Gordon *et al.* studied single agent erlotinib in patients with refractory, recurrent, EGFR positive epithelial ovarian tumors who had failed taxane and/or platinum-based chemotherapy: 34 patients received daily erlotinib for up to 48 weeks or until disease progression or dose-limiting toxicity. ORR was 6% (95% CI, 0.7-19.7%) and median overall survival (OS) was eight months (95% CI, 19.8-53.5%). PFS was not analyzed. Of interest, patients with a rash survived significantly longer than those without a rash ($P=0.009$) (7). In one of several phase II Gynecologic Oncology Group trials (GOG) of single agent biologics upon persistence or recurrence of ovarian or primary peritoneal cancer, Schilder *et al.* assessed gefitinib in 30 patients and found minimal activity with only four patients experiencing a PFS ≥ 6 months (including one patient achieving a partial response (PR). The median PFS of 2.17 months did not meet GOG criteria for further study (in contrast with the subsequent study of bevacizumab). Archival tumor tissues were assessed for expression of EGFR by immunohistochemistry (IHC): positive expression (IHC 1+ or higher) was seen in 11 (42%) of the tumors. The four patients with prolonged PFS had tumors with some EGFR-positivity, albeit 1+ or 2+ intensity in $<10\%$ of the tumor cells in 3 including the patient with PR. EGFR mutation analysis for the tyrosine kinase domain encoded by exons 18 to 21 of EGFR was conducted: of 25 specimens assessed, only the patient with PR had a EGFR mutation (8). In another GOG ovarian biologic queue study, Campos *et al.* evaluated canertinib (CI-1033), a 4-anilinoquinazoline that acts irreversibly at the adenosine triphosphate (ATP) binding site of the erbB receptor family member: no complete responses (CRs) or PRs were observed. Median PFS was 2.2 months. In an analysis of archived tumor samples, there was no relationship between tumor expression of any of the erbB subtypes and disease stabilization or OS (9).

Lapatinib, a dual EGFR/human epidermal growth factor receptor 2 (HER2/*neu*) inhibitor, was studied with carboplatin and paclitaxel in stage III or IV relapsed ovarian cancer. ORR was 50% in 21 patients (10). Single agent lapatinib studied

in the GOG biologic queue in persistent or recurrent disease failed to show any objective responses in 25 patients with a median PFS of 1.8 months (11). Since topotecan resistance may result from drug efflux by P-glycoprotein (Pgp), breast cancer resistance protein (BCRP; ABCG2), and survival signals initiated by EGFR family members and lapatinib enhances the efficacy of topotecan *in vitro*, the combination was explored in a phase I trial: lapatinib and topotecan was given to 37 patients with solid tumors including ovarian cancer and SD seen in 18 patients (12). A phase II trial in 39 patients with recurrent ovarian cancer after first line chemotherapy yielded a disappointing 14% PR (13). Warner *et al.* evaluated topotecan and erlotinib in six patients previously failing bolus topotecan. Topotecan as a continuous infusion over 9-10 days every 3 weeks and erlotinib on days 1-10 every 3 weeks resulted in one patient achieving PR by CA-125 criteria. Notably, dermatologic toxicity was less than expected in this intermittent schedule (14).

Studies with antibodies against EGFR

Monoclonal antibodies may be designed to prevent ligand binding, promote antibody-receptor complex internalization and subsequent degradation, prevent activation of EGFR-associated, downstream signaling pathways, and to induce apoptosis (15). Cetuximab, the first anti-EGFR monoclonal antibody in clinical trials, has been evaluated in ovarian cancer. In a GOG study, Secord *et al.* assessed cetuximab and carboplatin in a relapsed platinum-sensitive population: 28 patients received cetuximab (initial dose of 400 mg/m² intravenously on cycle 1 day 1 followed by weekly infusions of 250 mg/m²) and carboplatin at an AUC of 6 every 21 days. ORR was 34.6% and the median time to progression was 9.4+ months (range 0.9-22.2+ months); response did not relate to the severity of cetuximab-induced rash. Archival tissue for EGFR expression by IHC showed positive EGFR expression ($\geq 1+$) in 92.9% of patients and only 2 (7.1%) were negative for EGFR but both responded. Response rates for patients with EGFR positive tumors were 60%, 40% and 33% for 1+, 2+ and 3+ EGFR staining, respectively, showing that staining intensity for EGFR was not predictive of response to cetuximab and it was hypothesized that high intensity may actually predict for cetuximab resistance (16). In another GOG study, Konner *et al.* evaluated cetuximab, paclitaxel and carboplatin: 40 patients received paclitaxel and carboplatin on day 1 and cetuximab on days 1, 8, 15 (400 mg/m² on day 1 and 250 mg/m² for subsequent doses) on a 21 day cycle yielding a median PFS of 14.4 months and a PFS at 18 months of 38.8% (17). In the biologic queue, Schilder *et al.* evaluated single agent cetuximab in 25 patients: one patient achieved a PR and nine patients had stable disease (SD) and did not achieve the required minimal

activity for future study by GOG with a median PFS of 2.1 months (18). EMD72000 (matuzumab), a humanized anti-EGFR monoclonal antibody, was investigated in a phase II study of 37 heavily pre-treated patients with platinum-resistant disease: no responses were seen (19).

Erlotinib as consolidation

In this randomized phase III trial, Vergote *et al.* evaluated the use of maintenance erlotinib in patients with ovarian, peritoneal, or fallopian tube cancer with response or SD after primary therapy (4). Notably, in NSCLC, erlotinib had shown significant prolongation of survival in a placebo-controlled maintenance trial (20). Eligible patients were histologically confirmed high risk International Federation of Gynecology and Obstetrics (FIGO) stage I (grade 3, aneuploidy grade 1 or 2, or clear cell) or stages II to IV epithelial ovarian, primary peritoneal or fallopian tube cancer. First-line therapy had to include 6-9 cycles of a platinum derivative alone or in combination with other agents. At the end of first-line therapy, patients had to have a CR, PR or SD as evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) criteria and/or by the Gynecological Cancer Intergroup (GCIIG) criteria for cancer antigen 125 (CA 125)-based evaluation. Of 835 patients, 67% had stage III disease and 18% stage IV disease; they were randomly assigned to maintenance erlotinib 150 mg orally daily for two years or until disease progression (n=420) or to observation (n=415). The primary endpoint was PFS. The trial assumed a PFS of 15 months in the control arm and an increase in PFS in 25% for the experimental (erlotinib) arm (i.e., from 15 to 18.75 months) (4).

The median follow-up was 51 months. In the erlotinib arm, 107 patients (25.8%) stopped treatment due to unacceptable adverse events at a median of 244 days (range 5-934 days) and 280 (50.1%) required dose modification mainly due to diarrhea or rash. In intention-to-treat analyses, PFS and OS were similar between the two groups. PFS was 12.7 and 12.4 months for the erlotinib and observation arms, respectively (HR adjusted for stratification factors, 1.05; 95% CI, 0.90-1.23; P=0.525). Progression was noted in 316 patients in the erlotinib arm and 306 in the observation arm. OS was 50.8 and 59.1 months for the erlotinib and observation arm, respectively (HR, 0.99; 95% CI, 0.81-1.20; P=0.903). In subgroup analyses (age, FIGO stage, volume of residual tumor after primary surgery, type of response after first-line chemotherapy and type of first-line chemotherapy), there was no apparent superiority for either one of the treatment arms. Global health/quality of life (QOL) scores did show a significant difference between the two treatment arms during the first year (P=0.0102) in favor of the observation arm (4).

Archival tumor tissue, sampled before and/or during first-

line chemotherapy, obtained for all patients was used to evaluate EGFR overexpression by IHC, EGFR copy number by fluorescence *in situ* hybridization (FISH) and to perform EGFR mutation analyses. IHC and FISH were performed in 248 patients (30%) and positive staining by IHC was present in 90 patients (36.3%); 41 patients (32.8%) in the erlotinib arm and 49 patients (39.8%) in the observation arm. The FISH assay for EGFR was positive in 66 patients (26.6%); 30 patients (24%) in the erlotinib arm and 36 patients (29.3%) in the observation arm). No correlation was identified between EGFR staining and any of the clinicopathologic variables. In the erlotinib arm, there was no association between PFS, OS, and discontinuation of treatment and IHC staining or the FISH score. In the entire cohort, patients who were positive by FISH did have a worse OS compared to those who were negative (46.1 versus 67 months; HR, 1.56; 95% CI, 1.01-2.40; P=0.044). This was similarly seen in a PFS analysis: patients who were EGFR positive by FISH did have a shorter PFS than those who were negative (9.6 versus 16.1 months; HR, 1.57; 95% CI, 1.11-2.22; P=0.01). DNA mutation analysis was performed for 318 patients. The following mutations were demonstrated: EGFR (n=3); KRAS (n=9); NRAS (n=2); BRAF (n=2); and PI3KCA (n=12). In patients with a mutation, the PFS was longer than in those who did not experience a mutation (34 versus 12.2 months, HR, 0.49; 95% CI, 0.28-0.88; P=0.015). However, EGFR-related mutations did not predict for efficacy of erlotinib in the treatment arm (4).

In summary, this study showed no benefit of maintenance erlotinib when compared with standard management. No subgroups benefiting from erlotinib were identified; however, 26% of patients discontinued erlotinib due to toxicity. EGFR overexpression, increased EGFR copy number, or EGFR mutations were not predictive of erlotinib efficacy (4).

Conclusions and future directions

The EGFR pathway has been extensively studied in ovarian cancer with disappointing results and at present, there is no role for EGFR targeted agents in ovarian cancer outside of clinical trials. The EGFR pathway is active and associated with a worse prognosis but EGFR inhibitors have demonstrated minimal therapeutic activity in ovarian cancer. Identifying patient subsets who will benefit from EGFR TKIs has not, at present, been feasible. Mutation analysis as in NSCLC is not applicable to ovarian cancer: in The Cancer Genome Atlas (TCGA), out of 429 serous ovarian cancer patients, somatic mutations and germline variants in *EGFR* were reported to be low (<1.3% and <0.3%, respectively) (21). This is similar to what was seen in Vergote's study: only 3/318 patients had mutations in EGFR (4).

We await greater insights into elucidating the mechanisms of resistance to EGFR inhibitors and how they interact with

other pathways before additional clinical studies. Anti-EGFR therapy resistance mechanisms include the production of EGFR-activating ligands, receptor mutations, constitutive activation of downstream pathways and activation of alternative signaling pathways (3). Primary and long-term cultured ovarian cancer cells are quite resistant to anti-EGFR-targeted therapies and EGFR TKIs fail to augment natural killer cell cytotoxicity in *in vitro* models (22). Activation of the EGFR pathway results in transduction of EGFR signals, including the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway cascade involved in cellular motility, proliferation, differentiation, survival and tumorigenesis (3). In fact, AKT is frequently overexpressed in ovarian cancer (23) and its activation has been proposed as a mechanism of resistance; dual inhibition of ovarian cancer cells in 3D spheroid cultures with BEZ235, a PI3K/mTOR inhibitor, and EGFR inhibitors PD168393 or gefitinib resulted in marked cell death (24). Similar cross-talk was demonstrated between EGFR and the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway that mediates the epithelial-mesenchymal transition and enhances migration (25). Finally, endothelin-1 (ET-1) and the selective endothelin-A-receptor (ET_AR), a G protein coupled receptor, are overexpressed in ovarian carcinomas. The autocrine ET-1/ET_AR axis triggers multiple signaling pathways, which are involved in cell proliferation, survival, angiogenesis and invasion. ET-1 can also transactivate EGFR through a Src-dependent mechanism. ET-1 induced rapid Src and EGFR phosphorylation and caused an increase in activation of mitogen-activated protein kinase (MAPK) and AKT in HEY cells (ovarian cancer cell line). Treatment of HEY cells with gefitinib reduced ET-1 induced Src and EGFR activation; however, ET-1 mediated MAPK and AKT activation was incompletely reduced. ZD4054, an endothelin receptor antagonist, combined with gefitinib did result in greater inhibition of all of these pathways, suggesting that dual targeting is critical (26).

In conclusion, this featured phase III study showed no benefit of maintenance erlotinib in ovarian cancer. This begs the question: is EGFR a true oncogenic 'driver' in ovarian cancer? EGFR mutations are rarely present in ovarian cancer and no association has been demonstrated between efficacy of EGFR-targeted therapies and EGFR overexpression and/or amplification in ovarian cancer. Successful targeting of the pathway for ovarian cancer has not yet been achieved, but perhaps may emerge from one of the following therapeutic strategies: (I) further studying the tumor microenvironment and potential inhibition of EGFR ligands; (II) inhibiting EGFR by antibodies targeting different members of the EGFR family; (III) utilizing both an antibody and a TKI to EGFR concomitantly; and (IV) using dual inhibitors of

EGFR and other receptors relating to angiogenesis (either by a multi-kinase inhibitor or more than one molecule). These approaches may help us to gain greater insight on how EGFR contributes to cancer growth, which will be critical if we hope to identify any clinical benefit.

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References

1. Smolle E, Taucher V, Pichler M, et al. Targeting signaling pathways in epithelial ovarian cancer. *Int J Mol Sci* 2013;14:9536-55.
2. Lee CK, Brown C, Gralla RJ, et al. Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis. *J Natl Cancer Inst* 2013;105:595-605.
3. Siwak DR, Carey M, Hennessy BT, et al. Targeting the epidermal growth factor receptor in epithelial ovarian cancer: current knowledge and future challenges. *J Oncol* 2010;2010:568938.
4. Vergote IB, Jimeno A, Joly F, et al. Randomized phase III study of erlotinib versus observation in patients with

- no evidence of disease progression after first-line platinum-based chemotherapy for ovarian carcinoma: a European Organisation for Research and Treatment of Cancer-Gynaecological Cancer Group, and Gynecologic Cancer Intergroup study. *J Clin Oncol* 2014;32:320-6.
5. Hirte H, Oza A, Swenerton K, et al. A phase II study of erlotinib (OSI-774) given in combination with carboplatin in patients with recurrent epithelial ovarian cancer (NCIC CTG IND.149). *Gynecol Oncol* 2010;118:308-12.
 6. Blank SV, Christos P, Curtin JP, et al. Erlotinib added to carboplatin and paclitaxel as first-line treatment of ovarian cancer: a phase II study based on surgical reassessment. *Gynecol Oncol* 2010;119:451-6.
 7. Gordon AN, Finkler N, Edwards RP, et al. Efficacy and safety of erlotinib HCl, an epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor, in patients with advanced ovarian carcinoma: results from a phase II multicenter study. *Int J Gynecol Cancer* 2005;15:785-92.
 8. Schilder RJ, Sill MW, Chen X, 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.
 9. Campos S, Hamid O, Seiden MV, et al. Multicenter, randomized phase II trial of oral CI-1033 for previously treated advanced ovarian cancer. *J Clin Oncol* 2005;23:5597-604.
 10. Rivkin SE, Muller C, Iriarte D, et al. Phase I/II lapatinib plus carboplatin and paclitaxel in stage III or IV relapsed ovarian cancer patients. *J Clin Oncol* 2008;25:5556.
 11. Garcia AA, Sill MW, Lankes HA, et al. A phase II evaluation of lapatinib in the treatment of persistent or recurrent epithelial ovarian or primary peritoneal carcinoma: a gynecologic oncology group study. *Gynecol Oncol* 2012;124:569-74.
 12. Molina JR, Kaufmann SH, Reid JM, et al. Evaluation of lapatinib and topotecan combination therapy: tissue culture, murine xenograft, and phase I clinical trial data. *Clin Cancer Res* 2008;14:7900-8.
 13. Lheureux S, Krieger S, Weber B, et al. Expected benefits of topotecan combined with lapatinib in recurrent ovarian cancer according to biological profile: a phase 2 trial. *Int J Gynecol Cancer* 2012;22:1483-8.
 14. Warner E, Liebes L, Levinson B, et al. Continuous-infusion topotecan and erlotinib: a study in topotecan-pretreated ovarian cancer assessing shed collagen epitopes as a marker of invasiveness. *Oncologist* 2014;19:250.
 15. Martinelli E, De Palma R, Orditura M, et al. Anti-epidermal growth factor receptor monoclonal antibodies in cancer therapy. *Clin Exp Immunol* 2009;158:1-9.
 16. Secord AA, Blessing JA, Armstrong DK, et al. 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. *Gynecol Oncol* 2008;108:493-9.
 17. Konner J, Schilder RJ, DeRosa FA, et al. A phase II study of cetuximab/paclitaxel/carboplatin for the initial treatment of advanced-stage ovarian, primary peritoneal, or fallopian tube cancer. *Gynecol Oncol* 2008;110:140-5.
 18. Schilder RJ, Pathak HB, Lokshin AE, et al. Phase II trial of single agent cetuximab in patients with persistent or recurrent epithelial ovarian or primary peritoneal carcinoma with the potential for dose escalation to rash. *Gynecol Oncol* 2009;113:21-7.
 19. Seiden MV, Burris HA, Matulonis U, et al. A phase II trial of EMD72000 (matuzumab), a humanized anti-EGFR monoclonal antibody, in patients with platinum-resistant ovarian and primary peritoneal malignancies. *Gynecol Oncol* 2007;104:727-31.
 20. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol* 2010;11:521-9.
 21. Kanchi KL, Johnson KJ, Lu C, et al. Integrated analysis of germline and somatic variants in ovarian cancer. *Nat Commun* 2014;5:3156.
 22. Gottschalk N, Kimmig R, Lang S, et al. Anti-epidermal growth factor receptor (EGFR) antibodies overcome resistance of ovarian cancer cells to targeted therapy and natural cytotoxicity. *Int J Mol Sci* 2012;13:12000-16.
 23. Loganathan S, Kandala PK, Gupta P, et al. Inhibition of EGFR-AKT axis results in the suppression of ovarian tumors in vitro and in preclinical mouse model. *PLoS One* 2012;7:e43577.
 24. Muranen T, Selfors LM, Worster DT, et al. Inhibition of PI3K/mTOR leads to adaptive resistance in matrix-attached cancer cells. *Cancer Cell* 2012;21:227-39.
 25. Colomiere M, Ward AC, Riley C, et al. Cross talk of signals between EGFR and IL-6R through JAK2/STAT3 mediate epithelial-mesenchymal transition in ovarian carcinomas. *Br J Cancer* 2009;100:134-44.
 26. Rosanò L, Cianfrocca R, Masi S, et al. Beta-arrestin links endothelin A receptor to beta-catenin signaling to induce ovarian cancer cell invasion and metastasis. *Proc Natl Acad Sci USA* 2009;106:2806-11.

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