**PIK3CA Pathway Mutations Predictive of Poor Response Following Standard Radiochemotherapy ± Cetuximab in Cervical Cancer Patients**

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**Abstract**

**Purpose:** EGFR is frequently overexpressed in cervical cancer, suggesting EGFR blockade as a promising treatment approach. Cetuximab, an anti-EGFR antibody, used conjointly with radiochemotherapy, was feasible in first-line treatment of cervix carcinoma limited to the pelvis.

**Experimental Design:** This randomized phase II trial enrolled 78 FIGO stage IB2–IIIB cervical cancer patients to either cisplatin-based radiochemotherapy alone (arm B, n = 38) or conjointly with a 6-week course of weekly cetuximab (arm A, n = 40). Brachytherapy was given to the pelvic mass. Primary endpoint was disease-free survival (DFS) at 2 years. EGFR expression and targeted sequencing were performed in 54 of 78 patients.

**Results:** Cetuximab over a 6-week period did not improve DFS at 24 months. At 31 months median follow-up, DFS was not significantly different (P = 0.18). Complete response at 4 to 6 months was strongly predictive for excellent DFS (log-rank test; P < 0.001). PIK3CA, KRAS, and STK11 mutations were observed in 22%, 4%, and 2% of patients, respectively. No tumor with a PIK3 pathway mutation showed complete response (0/8 in arm A and 0/6 in arm B), whereas 14 of 52 (27%) tumors without mutations did (P = 0.021). PI3K pathway-mutated tumors showed a trend toward poorer DFS (P = 0.06) following cetuximab (8/22) as compared with those following standard treatment only (6/18).

**Conclusions:** Similar to patients with head and neck cancer, patients with cervical cancer showed no gain in DFS at 2 years following a combined treatment of cetuximab with radiochemotherapy. Although treatment tolerance and compliance were satisfactory, it remains to be demonstrated whether maintenance therapy with cetuximab could be beneficial in selected patient groups.

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**Introduction**

The treatment and the outcome of locally advanced, Federation Internationale des Gynaecologists et Obstetricitres (FIGO) stage IB2–IIIB carcinoma to the cervix have not notably changed over the past 10 years (1). At the time the present trial was initiated, numerous publications suggested the importance of EGFR pathway activation in cervical cancers, as suggested by frequent EGFR gene overexpression and amplification, often in association with other EGFR family members (2, 3). More recently, EGFR gene amplification has been reported in as many as 20% of high-grade CIN and invasive carcinoma of a Chinese population from Nanjing (4) and was associated with intermediate–high levels of EGFR protein overexpression. In a large Dutch study, membrane staining of EGFR (P = 0.005) and cytoplasmic staining of activated pEGFR (P = 0.016) were independent predictors of poor response to chemoradiation (5). EGFR overexpression in cervical cancers appeared to correlate with poor prognosis following standard therapy in some studies (6–8), but not in all (9, 10). Alterations in downstream signaling pathways, such as the PI3K pathway (11), are likely to modify the prognostic relevance of membrane EGFR.

Although EGFR-TKI treatment (such as gefitinib or erlotinib) has been shown to be particularly effective in advanced nonsmall cell lung cancer (NSCLC) patients, whose tumors harbored...
Translational Relevance

Cetuximab has proven beneficial in the treatment of patients with Kras wild-type metastatic colorectal cancer (mCRC) and in non–small cell lung cancer patients. Our results show that the addition of cetuximab to standard radiochemotherapy does not improve progression-free survival of patients with cervical cancer. Targeted sequencing on tumor material from our patient population showed patients with alterations in the PI3K pathway seem to have worst disease-free survival. Mutations in the PI3K pathway seem therefore to be an important parameter to predict absence of response to cetuximab.

activating EGFR mutations in the kinase domain (12, 13), no such mutations in exons 18–21, corresponding to the kinase domain, have been detected to date in cervical cancers (14–16). Cetuximab, a chimeric monoclonal antibody that binds to EGFR, disrupting its dimerization (17), had been proven beneficial in the treatment of patients with squamous cell carcinoma of the head and neck (SCCHN; refs. 18, 19), in Kras wild-type metastatic colorectal cancer (mCRC; ref. 20) as well as in NSCLC (21) patients. In an intention-to-treat analysis in NSCLC (Flex trial), tumor cell expression of EGFR (<40% vs. ≥40%) was not identified as a prognostic factor in relation to survival in the overall analysis (22). In cervical cancer, a recent phase I/II clinical trial in treatment naïve patients, documented the feasibility of concurrent cetuximab with cisplatin-based chemoradiotherapy to the pelvis; while the need for extended field radiotherapy, (EFRT) in combination with cisplatin and cetuximab was reported to be insufficiently tolerated (23). Objectives of the present trial were to assess the tolerance and the efficacy of the combining cetuximab with standard chemoradiotherapy, while also to assess outcome as a function of biologic parameters.

Patient assessments and follow-up

Clinical and imaging assessments using CT scan and MRI were made 2 weeks after the last dose of study medication (~ day 50), then one month after treatment completion (at 4–5 months) and scheduled every 4 months thereafter for the duration of the study period over 2 years. Tumor response was by MRI after treatment completion, according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria (24). For patients who underwent surgery (if feasible and in case of doubt about completeness of response), the response assessment was by pathology. A centralized blinded review of tumor imaging and pathology slides was performed. Patients were followed up every 4 months for 2 years.

Statistical analysis

The statistical sample size was determined using a Fleming one-step design under the hypothesis that the addition of cetuximab to radiochemotherapy would increase local regional control at 24 months from 50% (null hypothesis) to 75% (alternative hypothesis). Thirty-eight patients per arm were required to detect a difference with a 96% power and accepting a 7% type I error. Patients were randomly assigned to either standard therapy (arm B, n = 38) or standard therapy plus cetuximab (arm A = 40) using a technique of block permutations. Randomization was stratified by center and according to the pretreatment plan of surgery or no surgery following radiochemotherapy.

The primary endpoint was disease-free survival (DFS) at 2 years. Secondary endpoints were: complete response rates at 4 to 5 months, tolerance of the cetuximab combination with radiochemotherapy as defined by treatment-related serious adverse event (SAE) and adverse event (AE) rates occurring at any time, biologic criteria (mutations, detection of HPV DNA, overexpression of EGFR), and time from randomization to death of any cause or last follow up. The rates of overall survival (OS) and DFS were estimated using the Kaplan–Meier method and compared with log-rank tests. Cox proportional hazards regression models were used to perform multivariate analysis.

Mutational analyses: targeted sequencing

Fixed tumor material was available from 54 of 76 (72%) of patients and frozen samples from 27 patients (35%). Screening of hotspot mutations was performed by targeted sequencing using...
the Ion AmpliSeq cancer panel V1 in conjunction with the AmpliSeq library kit v2.0 and the Ion Torrent Personal Genome Analyzer (Life Technologies) for 54 patients for whom FFPE or frozen tumor samples were available.

**EGFR expression using IHC**

IHC analyses were performed using antibody directed against EGFR (mouse monoclonal; clone 31G7, Invitrogen; code 28005; dilution 1:200). The antibody was tested using Leica BOND III automation using the BOND Polymer Refine Detection (Leica biosystems).

**HPV typing**

Total DNA was used for HPV typing. Sufficient material was available for 54 (69%) of tumors which could be screened for the presence of HPV using generic GP5+/GP6+ primers by PCR. Specific primers were used for identification of HPV genotypes 6/11, 16, 18, 33, and 45.

**Results**

**Patient demographics**

Cetuxicol opened to accrual in March 2009 and completed accrual in July 2011. There was a balanced distribution according to pretreatment tumor size (MRI), parametrial involvement, PS, age, and smoking habits. There was no difference in pretreatment patient and tumor characteristics between both arms (Table 1). Two patients in arm A withdrew consent and were treated with standard therapy. Seventy-six patients were evaluable for tolerance and outcome (Fig. 1). One patient had FIGO Stage IB1 disease, but remained in the intention to treat analysis. Salvage surgery was carried out in 24 of 38 (65%) of patients evaluable for response in arm A and 26/38 (70%) in arm B following radiochemotherapy.

**Treatment compliance**

Compliance with protocol-specified radiation and drug therapy was satisfactory. In arm A, 9 patients were not able to receive the full CDDP as per schedule; 4 patients received only 4 or 5 weeks of cetuximab mainly as a result of grade 3 hematologic intolerance. In arm B, 11 patients received only 4 to 5 weeks of CDDP, for reasons of hematologic or renal tolerance. Overall, the median time between the start of RT-CT and the last day of treatment (brachytherapy, BT) was 53 days (range, 41–177) for all patients. The median doses of EBRT and brachytherapy received were similar in both arms (Supplementary Table S1).

**Table 1. Patient and tumor characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Arm A (cetuximab + ST)</th>
<th>Arm B (ST)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, min, max)</td>
<td>49.5 (23–74)</td>
<td>45.5 (25–75)</td>
<td>0.38</td>
</tr>
<tr>
<td>History of tobacco use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>21</td>
<td>24</td>
<td>0.34</td>
</tr>
<tr>
<td>–</td>
<td>19</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Postmenopause</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>19</td>
<td>14</td>
<td>0.34</td>
</tr>
<tr>
<td>–</td>
<td>21</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>History of oral contraception</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>16</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>–</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>MV</td>
<td>22</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Obesity (BMI ≥ 30)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>16</td>
<td>12</td>
<td>0.47</td>
</tr>
<tr>
<td>–</td>
<td>23</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>MV</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Histologic tumor type</td>
<td></td>
<td></td>
<td>0.60</td>
</tr>
<tr>
<td>Squamous</td>
<td>33</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>FIGO stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IB1</td>
<td>0</td>
<td>1</td>
<td>0.42</td>
</tr>
<tr>
<td>IB2</td>
<td>13</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>IIa</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td>18</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>IIIa</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>IIIb</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Median clinical tumor size</td>
<td>44 mm (range, 15–80)</td>
<td>40 mm (range, 20–80)</td>
<td>0.64</td>
</tr>
<tr>
<td>Median MRI tumor size</td>
<td>53.5 mm (range, 30–90)</td>
<td>47 mm (range, 24–85)</td>
<td>0.25</td>
</tr>
<tr>
<td>Anemia at diagnosis (Hb ≤ 10 g/L)</td>
<td>13</td>
<td>9</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviation: MV, missing value.

*Two patients withdrew consent early in their treatment schedule.*
Targeted sequencing controlled by Sanger Sequencing

Targeted sequencing of tumor DNA from 54 patients performed using the AmpliSeq 46 genes Cancer Panel on the Torrent PGM sequencer or using the SANGER technique for all PIK3CA and KRAS mutations. Hotspot mutations were detected in PIK3CA for 12 patients (22%), in KRAS for 5 patients (10%). The distribution was not significantly different (Table 2) between both arms. In addition, FBXW7 mutations were detected in 2 patients and BRAF, SMAD4, STK11, JAK3, and ATM in individual patients. Interestingly, one tumor with PIK3CA mutation also had BRAF and KRAS mutations. Another PIK3CA-mutated tumor also exhibited FBXW7 and SMAD4 mutations.

Treatment Efficacy

Primary endpoint

DFS at 24 months was 63% (95% confidence intervals; CI, 49%–80%; 14 events) in arm A and 76% (95% CI, 63%–91%; 9 events) in arm B. (Table 2).

Table 2. Targeted sequencing and response according to mutational status (n = 52 available for both response and mutational analysis)

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Tumors available for mutational analysis, n = 54 (%)</th>
<th>Arm A (n = 30)</th>
<th>Arm B (n = 24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA</td>
<td>12 (22)</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>BRAF</td>
<td>1 (3)</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>KRAS</td>
<td>5 (10)</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>STK11</td>
<td>1 (2)</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PIK3CA and KRAS</td>
<td>14 (26)</td>
<td>8</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>PIK3CA and KRAS and STK11</td>
<td>14 (26)</td>
<td>8</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Mutations</td>
<td>Complete response (n = 14/52)</td>
<td>Incomplete response (n = 38/52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIK3CA</td>
<td></td>
<td>12 (23%)</td>
<td>26 (50%)</td>
<td>0.042</td>
</tr>
<tr>
<td>No mutation detected</td>
<td></td>
<td>14 (27%)</td>
<td>24 (46%)</td>
<td>0.021</td>
</tr>
<tr>
<td>PIK3CA or KRAS</td>
<td></td>
<td>0 (0%)</td>
<td>14 (27%)</td>
<td></td>
</tr>
<tr>
<td>No mutation detected</td>
<td></td>
<td>14 (27%)</td>
<td>24 (46%)</td>
<td>0.021</td>
</tr>
<tr>
<td>One or several mutationsa</td>
<td></td>
<td>0 (0%)</td>
<td>16 (31%)</td>
<td>0.009</td>
</tr>
<tr>
<td>No mutation detected</td>
<td></td>
<td>14 (27%)</td>
<td>22 (42%)</td>
<td></td>
</tr>
</tbody>
</table>

aPIK3CA-KRAS-STK11-FBXW7-SMAD4-ATM-BRAF-JAK3.
events in arm B). With a median follow up of 31 months, no significant difference of DFS was shown between the two arms ($P = 0.18$; Fig. 2A). The 2-year OS was 83% for arm A (95% CI, 72%–96%; 7 events), and 87% for arm B (95% CI, 76%–98%; 5 events).

DFS as a function of classical clinical and histologic parameters

Outcome according to FIGO stage ($P = 0.19$) was not statistically different (only 7 stage III patients), but pelvic lymph node involvement was highly significantly associated with poorer DFS ($P = 0.0069$). Patients in the cetuximab arm (A) who developed acne did mildly better but this result was not statistically significant. Patient age, smoking habits ($\geq 10$), menopausal status, and obesity did not correlate with a difference in outcome; neither did IMRT versus conformal radiotherapy. Squamous-type histology patients had a better DFS than patients with nonsquamous-type histology, but not significantly so.

Clinical response evaluation

Early response evaluation at the end of the 6 weeks chemoradiation therapy seemed to be in favor the cetuximab treatment arm (7 objective responses in arm A and 3 in arm B). At the end of the complete treatment sequence and following central imaging review (at 4–5 months), response evaluation by either MRI (in the absence of surgery) or by histopathology in the case of surgery was similar for both arms. (Supplementary Table S3) Because of absent or poor quality MRI, 7 patients were not evaluable for response (4 in arm A and 3 in arm B). Twenty-four of 38 patients in arm A and 26 of 38 in arm B underwent salvage surgery. In arm A, 9 of 24 had residual disease on histology and 2 patients were node positive. In arm B, 12 of 26 patients had residual disease on histologic assessment and 1 had positive nodes. A total of 16 of 38 patients in arm A and 15 of 38 in arm B have achieved a complete response; only one patient had progressed early on in each treatment arm. Complete response (by either MRI or histopathology) strongly correlated with excellent DFS ($P = 0.0002$; Fig. 2B).

Associations between clinical outcome data and biologic parameters

Clinical response was available on 52 of 54 patients analyzed by targeted sequencing. In this subgroup analysis, 14 of 52 patients achieved a complete response and 38 of 52 did not. HPV could be assessed in 54 (69%) patients (Table 1). Among tumors with an oncogenic HPV, 26 carried no detectable mutation while 14 were associated with a mutation.

* Among PI3K pathway–mutated patients, 0 of 14 achieved a complete response at the 4 to 5 months evaluation ($P = 0.042$; Table 2). Patients who had achieved both a complete response (and whose tumors showed no PI3K pathway mutation) had a probability of a DFS at 24 months of 93% (80.3–100), contrasting with 50% (28.4–88) for those with either a PI3K pathway mutation or an incomplete response or both ($P = 0.097$; Fig. 3). Three out of 8 patients with a PI3K pathway mutation in arm A and 3 out of 6 in arm B had salvage surgery.
markers for activity. A recent meta-analysis in SCCHN cancer patients (68 studies involving 6,781 patients) suggested that elevated EGFR expression and above all elevated gene copy number were predictive for poor survival (26). Although recurrent/metastatic SCCHN and KRAS wild-type mCRC patients have been documented to benefit from cetuximab treatment with long-lasting survival differences and a gain of almost 10% at 5 years (19); only recently, did the Flex trial in advanced NSCLC show a subgroup of patients with high EGFR expression (22), to have a better OS following the combined treatment of chemotherapy/cetuximab (by 2.4 months; \( P = 0.011 \)) as compared with chemotherapy alone. A treatment interaction test assessing the difference in the HRs for OR between the EGFR expression groups suggested a predictive value for high EGFR expression (\( P = 0.044 \)). Similarly, a recent meta-analysis on NSCLC, showed the addition of cetuximab to chemotherapy to significantly improve OS, PFS, and response (29). In the present trial, cetuximab was administered only over a 6-week period, while in most NSCLC trials, the treatment duration was significantly longer, lasting up to 6 to 8 months. We cannot conclude that cetuximab is ineffective in all cervical cancer patients, keeping in mind that in our study, only a limited subpopulation of tumors had a significant EGFR overexpression/gene amplification, and that the exposure to cetuximab was only 6 weeks. Still, at the 7-week evaluation, we observed 7 complete responses in arm A and 3 in arm B. Negative results were reported recently from a phase III trial in patients with stage III or IV head and neck carcinoma (HNC) which, similarly to us, had tested the hypothesis that adding cetuximab to a radiation–cisplatin platform might improve PFS (30).

Of interest are our results showing alterations in the PI3K pathway to be an important factor in impeding complete response to standard therapy and to cetuximab since none of the tumors with one (or more) alterations, in the PIK3CA pathway showed a complete response following radiochemotherapy. Our findings are in agreement with data showing pretreatment alterations in gene expression in the PI3K/Akt signaling pathway (31) to correlate with a positive posttreatment PET scan in patients with cervical cancer. PIK3CA mutations seemed to retain a higher negative impact on PFS in the cetuximab-treated patients. Although the reason for this is not clear, similar results have been reported in metastatic colorectal cancer. KRAS mutations and PIK3CA/PTEN deregulation have been suggested to significantly correlate with resistance to cetuximab (32), whereas the absence of mutations in KRAS, NRAS, BRAF, and TP53 was correlated with improved outcome in patients treated with cetuximab, oxaliplatin, and UFT (33). Recent clinical evidence suggests reversible and adaptive transcriptional responses to drugs in this pathway (34).

We did not detect any EGFR mutations in the present patient population in accordance with previous reports in cervical cancer (14, 15). EGFR mutations had similarly been undetectable in HPV-positive SCCHN (T Seifert, ASCO 2013). Although EGFR mutations have been shown relevant for the clinical effect of small-molecular inhibitors in advanced NSCLC (12, 13), they may not be relevant for the clinical effect of cetuximab.

Molecular targeted therapies in cervical cancer remain presently inconclusive. Patients with KRAS and PIK3CA mutations (or PTEN loss) might benefit from therapies targeting downstream EGFR signaling such as PI3K and mTOR inhibitors. p-Akt has been suggested as a biomarker for poor prognosis (31). It also needs to be clarified how tumor cell alterations impact the tumor microenvironment to allow dual-targeting.
strategies, combining targeted antitumor drugs together with vaccines/antiviral strategies.

In conclusion, our results suggest that gene mutations may be an important parameter in predicting treatment response. It remains to be demonstrated whether a prolonged maintenance treatment with cetuximab might have a significant impact in a targeted cervical cancer population whose tumors have EGFR gene amplification/overexpression and absent mutations in the PI3K pathway. For a better understanding of the driver mutations in cervical cancer, we initiated the RAIDs project (Rational Approach and Innovative Drug selection) with the aim to assess dominant mutational events with new-generation sequencing techniques, signaling proteins expression, and activations with reverse-phase protein array, as well as studies on the tumor microenvironment in a prospective cohort of 700 patients. This project is supported by the European Commission in the frame of the FP7 program (http://www.raids-fp7.eu/).

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: A. de la Rochefordiere, P. Petrow, F. Joly, V. Fourchotte, B. Asselan, P. Beuzeboc, S.M. Scholl

References


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