Efficacy of Cetuximab in Metastatic Castration-Resistant Prostate Cancer Might Depend on EGFR and PTEN Expression: Results from a Phase II Trial (SAKK 08/07)

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Abstract

Purpose: The EGF receptor (EGFR) is overexpressed in the majority of metastatic castration-resistant prostate cancers (mCRPC) and might represent a valid therapeutic target. The combination of docetaxel and cetuximab, the monoclonal antibody against EGFR, has not been tested in patients with prostate cancer.

Experimental Design: Patients with mCRPC progressing during or within 90 days after at least 12 weeks of docetaxel were included in this phase II trial. Treatment consisted of docetaxel (75 mg/m² every 3 weeks or 35 mg/m² on days 1, 8, 15 every 4 weeks) in combination with cetuximab (400 mg/m² on day 1 and then 250 mg/m² weekly). The primary endpoint was progression-free survival (PFS) at 12 weeks defined as the absence of prostate-specific antigen (PSA), radiographic, or clinical progression. Evaluation of known biomarkers of response and resistance to cetuximab (EGFR, PTEN, amphiregulin, epiregulin) was conducted.

Results: Thirty-eight patients were enrolled at 15 Swiss centers. Median age was 68 years and median PSA was 212 ng/mL. PFS at 12 weeks was 34% [95% confidence interval (CI), 19%–52%], PFS at 24 weeks was 20%, and median overall survival (OS) was 13.3 months (95% CI, 7.3–15.4). Seven patients (20%) had a confirmed ≥50% and 11 patients (31%) a confirmed ≥30% PSA decline. About 47% of enrolled patients experienced grade 3 and 8% grade 4 toxicities. A significantly improved PFS was found in patients with overexpression of EGFR and persistent activity of PTEN.

Conclusions: EGFR inhibition with cetuximab might improve the outcome of patients with mCRPC. A potential correlation between EGFR overexpression, persistent expression of PTEN, and EGFR inhibition should be investigated further.

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combination with chemotherapy has shown significant prolongation of survival in metastatic colorectal cancer and non–small cell lung cancer (NSCLC). The response to cetuximab has been associated with several factors: in colorectal cancer with the lack of KRAS mutation (5), overexpression of the EGFR ligands amphiregulin and epiregulin (5), and persistent PTEN (6); and in NSCLC with EGFR overexpression (7).

Cetuximab has shown preclinical activity in prostate cancer models: in DU145 cell line, it inhibits growth by inducing G1 arrest (8); in both androgen-responsive and -independent cell lines, it blocks the EGF-induced receptor activation and induces internalization of the receptor (9). Cetuximab has also shown significant antitumor activity in animal models of prostate cancer and this effect was enhanced by simultaneous administration of paclitaxel (10).

This trial tested the hypothesis whether adding cetuximab to chemotherapy with docetaxel can re-induce a tumor response and hence prolong progression-free survival (PFS) in patients with metastatic docetaxel-refractory CRPC. Moreover, it explored the association of the efficacy of EGFR inhibition by cetuximab and known biomarkers of response/resistance to this monoclonal antibody.

**Materials and Methods**

**Experimental design**

Patients with mCRPC progressing during or after 12 weeks of docetaxel were included in this phase II trial. Treatment consisted of docetaxel (75 mg/m² every 3 weeks or 35 mg/m² every 4 weeks) in combination with cetuximab (400 mg/m² on day 1 and then 250 mg/m² weekly). The primary endpoint was PFS at 12 weeks defined as the absence of prostate-specific antigen (PSA), radiographic, or clinical progression. Evaluation of known biomarkers of response and resistance to cetuximab (EGFR, PTEN, amphiregulin, epiregulin) was conducted.

**Eligibility criteria**

Eligibility criteria included histologically documented adenocarcinoma of the prostate, metastatic disease; proven disease progression while on androgen deprivation therapy; received at least 12 weeks of docetaxel chemotherapy; and experienced progressive disease by PSA progression (confirmed PSA increase ≥ 25% above Nadir) or progression of metastases during docetaxel or within 90 days after stopping docetaxel treatment; World Health Organization (WHO) performance status 0 to 2; and adequate hematochemical (neutrophils ≥ 1,500/mm³, platelets ≥ 100,000/mm³), hepatic (bilirubin ≤ 1.5 × upper limit of normal (ULN), alanine aminotransferase (ALT) ≤ 2.5 × ULN), and renal function (calculated creatinine clearance ≥ 30 mL/min). Patients were excluded if they had neuropathy ≥ grade 2, known central nervous system metastases, radiotherapy within 2 weeks before inclusion, anti-androgen therapy not discontinued more than 6 weeks before inclusion, and if they had received prior treatment with drugs interacting with the EGFR pathway.

The trial was approved by the local ethics review boards and Swissmedic (Swiss agency for therapeutic products). It is registered at the NIH (www.clinicaltrial.gov; identifier number: NCT00728663). All patients gave informed consent.

**Treatment**

Patients were treated with the same docetaxel schedule they had received before registration into the trial. Hence, 2 different docetaxel schedules were administered: the every-3-week regimen consisted of docetaxel i.v. at a dose of 75 mg/m² administered over 1 hour on day 1 of each 21-day cycle and the weekly regimen of docetaxel i.v. 35 mg/m² on days 1, 8, and 15 every 28 days. Cetuximab was administered before docetaxel at an initial dose of 400 mg/m² i.v. over 120 minutes on day 1 and then on a weekly basis at a dose of 250 mg/m² i.v. over 60 minutes. Oral prednisone at a dose of 10 mg/d was administered continuously from day 1. Ongoing castration with luteinizing hormone releasing hormone (LHRH) analogues was mandatory for all patients (if not surgically castrated). Treatment was administered for a maximum of 24 weeks, until progression, unacceptable toxicity, or withdrawal of consent.

**Assessments and disease evaluations**

Screening assessments including computed tomographic (CT) scan of the chest, abdomen, and pelvis and a bone scan were recorded within 28 days of registration. All patients had repeated radiographic assessments every 12 weeks and PSA was measured every 4 weeks.

PFS was defined as the absence of disease progression for biochemical PSA progression, progression of measurable disease, progression of bone lesions, or clinical progression. PSA progression was defined as an increase of ≥25% above Nadir or baseline. The increase had to be ≥ 2 ng/mL and had
to be confirmed 3 or more weeks later. PSA response was defined as decrease in PSA of at least 50% from baseline (PSA, 50%) or of at least 30% from baseline (PSA, 30%).

Response of measurable disease was assessed by investigators according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0. For evaluation of bone metastases in bone scans, the guidelines of Prostate Cancer Working Group 2 (PCWG2) were applied (11).

Adverse events were graded according to National Cancer Institute’s Common Terminology Criteria of Adverse Events, version 3.0.

Translational research
All patients who received at least one dose of trial treatment were eligible for inclusion into the translational research analysis. A separate informed consent was obtained; participation in the translational research part was not required for participation in the trial itself. Existing biopsies from the participating patients were collected at the end of the trial at Institute for pathology of University Hospital Basel (Basel, Switzerland).

Immunohistochemistry
All biopsies were fixed in 4% buffered formalin and were embedded in paraffin. Fresh sections (4-μm) of the paraffin-embedded prostate biopsies were used for immunohistochemical staining with 6 different antibodies. We used standard indirect immunoperoxidase procedures on the Ventana BenchMark XT autostainer (Roche Diagnostics). The following primary antibodies were used: amphiregulin (R&D, goat polyclonal, dilution 1:20, microwave pretreatment for 60 minutes at 98°C), epiregulin (R&D, goat polyclonal, dilution 1:50, pronase pretreatment for 15 minutes), EGFR (Ventana Medical Systems, clone c026, mouse monoclonal, prediluted, protease pretreatment), ERG [Biocare Med, clone 9FY, mouse monoclonal, dilution 1:10, pretreatment with Ventana cell conditioning 1 (CC1)], PTEN (Novocastra, clone 28H6, mouse monoclonal, dilution 1:100, pretreatment with Ventana cell conditioning 1 (CC1)], SPINK1 (Abcam, mouse monoclonal, prediluted, protease pretreatment), ERG [Biocare Med, clone 9FY, mouse monoclonal, dilution 1:10, pretreatment with Ventana cell conditioning 1 (CC1)], PTEN (Novocastra, clone 28H6, mouse monoclonal, dilution 1:100, pretreatment with CC1), and SPINK1 (Abcam, mouse monoclonal, dilution 1:800, pretreatment with CC1). One pathologist (L. Bubendorf), who was blinded to the clinical follow-up data, viewed all immunostained slides. A case was considered positive of ERG and SPINK1 when any tumor staining was present. The staining intensity of all other markers was visually scored and stratified into 4 categories using a kit for archival material (AmpTec GmbH) as previously described (13). RNA qualities were assessed on an Agilent 2100 Bioanalyzer (Agilent Technologies, Inc.). The isolated RNA was tested for the following 6 genes: amphiregulin, epiregulin, EGFR, ERG, SPINK1, and PTEN. Three control genes were used for internal reference and normalization [glyceraldehyde-3-phosphate dehydrogenase (GAPDH), RPL13A, and UBC]. The genes were measured by quantitative real time (RT)-PCR using a one-step protocol (Invitrogen) on a ViiA 7 instrument (Applied Biosystems). Raw cycle threshold (C) values were normalized against the mean expression of GAPDH, RPL13A, and UBC.

Statistical design and analysis
All patients who received at least one dose of trial treatment with cetuximab and docetaxel were considered evaluable for efficacy. A Simon optimal 2-stage design was used for this single-arm phase II multicenter trial (14). The primary endpoint was PFS at 12 weeks. The trial therapy would be considered promising if the proportion of patients with a PFS at 12 weeks was 30% or more and uninteresting if it was 10% or less. With 90% power and 5% significance level, the total sample size was calculated to be 35 patients. Stage 1 accrued 18 evaluable patients: if 2 patients or less experienced PFS at 12 weeks, the trial would be stopped early, otherwise another 17 patients were to be registered. At the end, if the total number reaching the primary endpoint was less than or equal to 6, the treatment would be rejected. Herndon modification was applied to continue accrual during the interim analysis (15).

Secondary endpoints included PFS at 24 weeks, PFS, overall survival (OS), PSA response with ≥50% decline and ≥30% decline, assessment of measurable disease according to RECIST, and assessment of bone lesions and toxicity. Adverse events were summarized by event type and grade over the total number of patients (worst recorded adverse event grade per patient).

Time-to-event endpoints were analyzed by Kaplan–Meier methods, groups were compared using the log-rank test. Numerical values were compared between groups using the Wilcoxon rank-sum test. For categorical data, the Fisher exact test was applied. For the biomarker data, patients with missing values were omitted from the analyses and cutoff values were determined using recursive partitioning and regression trees and confirmed by the maximally selected log-rank statistics method. P values are 2-sided, not adjusted for multiple testing, and considered significant if <0.05. The data were analyzed in SAS (Statistical Analysis Systems Institute Inc., version 9.2) and the free statistical software package R version 2.13.1 or later (16).

Results
Patient characteristics
Between July 2008 and September 2009, 38 patients were enrolled. Three patients did not receive a complete dose of any trial treatment (2 patients experienced grade 3/4 hypersensitivity reaction within the first minutes of the first dose of cetuximab and one patient had to undergo surgery for spinal cord compression before start of trial medication)
and were therefore not evaluable for efficacy as per protocol. Baseline characteristics of the evaluable patients are presented in Table 1. The median follow-up time was 25.4 months.

### Treatment administration

A total of 157 cycles of trial treatment were given to 35 patients. Median number of cycles was 4 (range, 1–8) and median treatment duration was 82 days (range, 20–180). Twenty-six patients (74%) received the every-3-week and 9 (26%) the weekly docetaxel schedule. About 88% of docetaxel cycles and 82% of cetuximab cycles were given without dose reduction, omission, or delay.

### Activity of cetuximab in combination with docetaxel

Confirmed PFS at 12 weeks according to definition was achieved in 12 of the 35 patients [34%; 95% confidence interval (CI), 19%–52%]. Therefore, the null hypothesis (PFS at 12 weeks < 10%) could be rejected. PFS at 24 weeks was achieved in 7 patients (20%; 95% CI, 8%–37%). The median PFS was 2.8 months (95% CI, 2.4–3.2 months). The median OS was 13.3 months (95% CI, 7.3–15.4 months). The Kaplan–Meier curves for PFS and OS are shown in Fig. 1A.

A confirmed ≥50% PSA decline was observed in 7 patients (20%) and a confirmed ≥30% PSA decline in 11 patients (31%). Full PSA response data (confirmed and unconfirmed) are summarized in the waterfall plots in Fig. 2. For one patient, there was only one PSA baseline measurement available, hence no change in PSA could be calculated.

In patients with measurable disease at baseline (n = 24), one patient showed a partial remission (4%), 13 patients had stable disease (54%), 6 patients were progressive (25%), and in 4 cases no reassessment was done (17%). Five patients (14%) had progressive bone metastases at the 12-week bone scan.

An unplanned subgroup analysis was conducted looking at the efficacy of the combination of docetaxel and cetuximab in patients who developed any form of skin toxicity at any grade (n = 29) compared with patients who did not (n = 6). Figure 1B shows a statistically significant longer median PFS of 2.8 (95% CI, 2.5–4.4) versus 1.8 (95% CI, 0.9–2.8) months (P = 0.0002) and median OS of 14.4 (95% CI, 8.2–17.4) versus 3.7 (95% CI, 1.5–12.0) months (P = 0.0001) for patients developing any skin toxicity.

### Toxicity

Toxicity observations are based on all enrolled patients who started trial treatment (n = 37). Eighteen patients

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**Table 1. Evaluable patient characteristics at baseline**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>(N = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: median (range), y</td>
<td>68 (45–82)</td>
</tr>
<tr>
<td>PSA: median (range), ng/mL</td>
<td>212 (4.4–8,898)</td>
</tr>
<tr>
<td>WHO performance status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9 (26)</td>
</tr>
<tr>
<td>1</td>
<td>21 (60)</td>
</tr>
<tr>
<td>2</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Site of metastasis, n (%)</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>31 (89)</td>
</tr>
<tr>
<td>Lymph node</td>
<td>22 (63)</td>
</tr>
<tr>
<td>Visceral</td>
<td>12 (34)</td>
</tr>
<tr>
<td>Number of prior docetaxel regimens, n (%)</td>
<td></td>
</tr>
<tr>
<td>1 prior regimen</td>
<td>23 (65)</td>
</tr>
<tr>
<td>2 prior regimens</td>
<td>9 (26)</td>
</tr>
<tr>
<td>3 prior regimens</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Best response to last docetaxel therapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>18 (51)</td>
</tr>
<tr>
<td>Progression</td>
<td>9 (26)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (23)</td>
</tr>
</tbody>
</table>
(47%) experienced a total of 23 serious adverse events (SAE) during the trial. Eleven of the 23 SAEs were attributed to the trial treatment. Twenty of the 37 patients (53%) had treatment-related grade 3 and 3 patients (8%) grade 4 toxicities. Table 2 lists all observed grade 3, 4, and 5 toxicities. Two patients died during trial treatment because of infections. One of the cases was associated with neutropenic sepsis.

Translational research

For an overview of the available samples and successfully conducted tests with the respective cut-off values, refer to the flow diagram presented in Fig. 3 (REMARK diagram; ref. 17). Confirmation of the cut-off values with the maximally selected log-rank statistics method found to be exactly the same as the cut-off in 6 of 8 markers, and in 2 cases (PCR for PTEN and EGFR), the cut-off was selected as neighboring value.

**Immunohistochemical and molecular analysis**

In an exploratory analysis, the expression of the biomarkers EGFR, PTEN, amphiregulin, epiregulin, and SPINK1+/ERG− was correlated with the clinical efficacy parameters of PFS, OS, and PSA response. Overexpression of EGFR or preserved/elevated expression of PTEN correlated significantly with PFS in molecular (for EGFR, \( P = 0.005 \); for PTEN, \( P = 0.0003 \)) and immunohistochemical analysis (for EGFR, \( P = 0.01 \); for PTEN, \( P = 0.02 \)). For patients with higher levels of both EGFR and PTEN (\( n = 16 \) in immunohistochemistry, \( n = 13 \) in PCR), the PFS is even more significantly improved (Fig. 4). For OS, a statistically significant difference is only observed for preserved RNA

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**Table 2. Drug-related toxicities (worst grade observed per patient, \( n = 37 \))**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reaction to cetuximab</td>
<td>1 (3)</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (3)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>1 (3)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>1 (3)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Bowel perforation and fistula formation</td>
<td>1 (3)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>1 (3)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (3)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (5)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (11)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Leucopenia</td>
<td>2 (5)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 (8)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Neutropenic fever</td>
<td>1 (3)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>—</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>1 (3)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (5)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Pulmonary infection without leucopenia</td>
<td>—</td>
<td>—</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>1 (3)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Septicemia with leucopenia</td>
<td>—</td>
<td>—</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Skin toxicity (total)</td>
<td>10 (27)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>1 (3)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Erysipelas</td>
<td>1 (3)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Dermatitis exfoliativa</td>
<td>1 (3)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Folliculitis</td>
<td>1 (3)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Hand foot syndrome</td>
<td>2 (5)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Periorbital dermatitis</td>
<td>1 (3)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 (3)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>2 (5)</td>
<td>—</td>
<td></td>
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</tbody>
</table>
expression of PTEN \((P = 0.02)\). Increased expression of EGFR and PTEN appears positively associated with improved PSA response as shown in the waterfall plots in Fig. 2. Overexpression of amphiregulin showed a superior benefit for PFS and OS in the PCR measurements but not by immunohistochemistry. Immunohistochemical or molecular expression of epiregulin or SPINK1 \(^+\)/ERG \(^-\) did not correlate with efficacy parameters (data not shown).

**Discussion**

To the best of our knowledge, this is the first trial testing the combination of the standard chemotherapy drug docetaxel with the monoclonal antibody cetuximab in patients with advanced prostate cancer. The trial was conducted in a population of pretreated patients with docetaxel-resistant mCRPC (defined as progression during docetaxel or within 90 days after docetaxel) at a time when no standard treatment options for these patients existed. Our results have to be distinguished from studies who looked at docetaxel retreatment in patients who experienced response to prior docetaxel and would be considered docetaxel-sensitive (18). Two articles have been published comparing different second-line chemotherapy regimens in patients resistant to docetaxel (19, 20): The treatments included monotherapies with mitoxantrone, ibahepilone, or satraplatin or combination treatments including carboplatin/docetaxel or carboplatin/etoposide. In these trials, a PSA response rate \(\geq 50\%\) of 17\%–23\% and median PFS between 2.1 and 3 months was reported, very similar to our trial. We also report a better OS for patients who develop any form or grade of skin toxicity. Of note, however, is the small number of only 6 patients without skin toxicity and these patients experienced an extremely short PFS and OS so that these results have to be interpreted with caution.

While there is no substantial advantage of using cetuximab in an unselected group of patients with mCRPC, there might be subgroups that derive more benefit. The most interesting information in this trial comes from the immunohistochemical and molecular analyses with regard to known factors of response/resistance to EGFR inhibition. Our results suggest that patients whose tumors have EGFR overexpression and PTEN persistence had a better outcome when treated with the monoclonal antibody against EGFR, cetuximab. So far despite some promising preclinical results, EGFR inhibition in mCRPC has mainly resulted in negative experiences. Single-agent trials with the EGFR-tyrosine kinase inhibitors (TKI) gefitinib (21) and erlotinib (22, 23) or the monoclonal antibody panitumumab (24) did not achieve any significant PSA response. Two other trials with cetuximab in combination with chemotherapy for patients with advanced prostate cancer have been presented earlier (25, 26): The combination of cetuximab with doxorubicin was associated with minimal PSA declines (25) and the combination of cetuximab with mitoxantrone did not show a benefit when compared with mitoxantrone alone (26). When assessing the entire patient population, our trial showed similar results: although the null hypothesis could be rejected, neither the PFS nor the PSA response rates indicate clinical usefulness especially in the presence of...
considerable toxicity of the study treatment. However, it is well known that EGFR inhibition in an unselected patient population is not a useful approach: lack of KRAS mutation, overexpression of the ligands amphiregulin and epieregulin, persistence of PTEN, and overexpression of EGFR have been shown to be predictive markers for response to cetuximab in colorectal or NSCLCs, respectively (5–7).

While KRAS mutations are rare in prostate cancer (27), EGFR overexpression and the importance of PTEN are well documented (3, 28–30). PTEN (phosphatase and tensin homologue deleted from chromosome 10) is a tumor suppressor gene that negatively modulates the phosphotidylinositol 3-kinase (PI3K)/AKT signaling transduction pathway that promotes tumor growth, proliferation, and survival. Loss of PTEN is correlated in prostate cancer with development of castration resistance, chemoresistance, and poor prognosis (28–30). Complete loss is found in 15% to 20% of localized disease and 30% of metastatic disease (31). The influence of PTEN expression on cell response was tested in PC3 prostate cancer cells that are KRAS wild-type, PTEN-null, and EGFR-overexpressing: it was shown that reintroduction of PTEN could significantly reduce the constitutive overexpression of p-AKT downstream kinases (p-GSK3β and p-P70S6) and p-ERK1/2 which led to significantly restored cetuximab-induced cell growth inhibition and induction of apoptosis (32). Therefore, patients with maintained PTEN expression might respond better to cetuximab-based treatment, and our results support this preclinical hypothesis. Apart from PTEN persistence, we show that the benefit from EGFR-targeted treatment is increased in presence of combination with higher EGFR levels. The question remains open: whether EGFR overexpression by itself would be a valid therapeutic target as might be suggested. In view of the discussed pathways and the importance of PTEN, this appears unlikely but our sample size is too small to draw further conclusions. Recently, a preclinical study reported attenuated tumor growth with cetuximab in a SPINK1+/ERG− prostate cancer mouse model (33), raising speculation about a possible new target for this subset of patients. Our results could not confirm this finding with no difference in PFS for patients with SPINK1+/ERG− prostate cancer according to immunohistochemical analysis.

Interestingly, we could show the same correlations for PTEN and EGFR in the immunohistochemical as in the molecular analysis. This suggests that the methods used to extract RNA from prostate cancer tumor tissue as described and established earlier for breast cancer tissue by the work of Oberli and colleagues (13) are also valid for prostate cancer. Provided that the tumor tissue is adequately sampled by an experienced pathologist, the RNA isolated from the formalin-fixed, paraffin-embedded prostate cancer tissue is suitable for molecular profiling.

Since the completion of this trial in 2009, several different new treatment options have shown a significant survival benefit for patients with mCRPC: they include the CYP-17 inhibitor abiraterone (34), the novel anti-androgen enzalutamide (35), the taxane cabazitaxel (36), the cellular immunotherapy with sipuleucel-T (37), as well as the radionuclide radium-223 (38). Clearly, the new therapies targeting the androgen receptor (AR) pathway will become widespread but eventually the disease progresses in the majority of patients and some patients are primarily refractory to these treatments. In these subgroups of patients, inhibition of EGFR in combination with a cytotoxic drug might play an important role.

The major limitations of our analyses include the setting of a single-arm phase II trial and the small sample size for translational research. No definitive conclusion can be drawn from these results about the predictive value of
assessing PTEN function and EGFR overexpression for response to cetuximab in patients with mCRPC. PTEN is also known to be a prognostic factor for better outcome (29), and our results might simply be due to generally better prognosis or maintained chemosensitivity. With regard to EGFR overexpression, however, this represents a negative prognostic factor at least in early-stage disease: a recent study showed a significantly increased risk of biochemical relapse in patients with high expression of EGFR (39). Another limitation is that the translational research was conducted on prostate biopsies obtained at the time of diagnosis. As outlined above, it is well known that the expression of EGFR can change with progression of disease (3) and occurrence of complete PTEN loss increases (31). Another point is the definition of docetaxel-resistant patients that is not agreed upon: by choosing a rather long 90-day window, we may have introduced heterogeneity by including patients who would have responded to docetaxel retreatment alone (18). On the other hand, we included PSA progression only in the primary endpoint and this could possibly have led to an underestimation of the benefit of the trial treatment.

In summary, the results of this trial for the whole patient population are comparable with those of other second-line phase II results with conventional chemotherapy in the treatment of docetaxel-refractory mCRPC. However, in the subgroup of patients with both EGFR overexpression and preserved PTEN, a signal of efficacy could be observed from the addition of cetuximab. Our observation correlates well with recent preclinical research and with results from studies in patients with colorectal cancer or NSCLCs and should therefore be investigated prospectively to clarify the clinical usefulness of the combination for the subgroup of patients with mCRPC selected by EGFR and PTEN status.

Disclosure of Potential Conflicts of Interest

R. Cathomas has a consultant role and research funding (for prostate cancer) from Sanofi-Aventis. D.R. Berthold has honoraria and research funding from and is a consultant/advisory board member of Sanofi-Aventis. L. Bubendorf has a consultant role and honoraria from Merck. S. Gillessen has a consultant role for Novartis, Sanofi-Aventis, Jansen Cilag, Pfizer, and Takeda-Millenium. R. Schiess is employed as the CEO and has ownership interest (including patents) in ProteoMedix AG. R. von Moos has a commercial research grant and honoraria from speakers bureau from Amsen and Roche and is a consultant/advisory board member of Amsen, Roche, Bristol Myers Squibb, Merck, and Novartis. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Conception and design: R. Cathomas, C. Rothermundt, L. Bubendorf, P. Brauchli, D.R. Berthold, R. von Moos, S. Gillessen
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