Outcomes of Patients with Metastatic Cervical Cancer in a Phase I Clinical Trials Program

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Abstract. *Background: We evaluated clinical outcomes of patients with metastatic cervical cancer referred to a Phase I Clinical Trials Program. Patients and Methods: We reviewed the electronic medical records of 54 consecutive phase I patients with metastatic cervical cancer over 6.5 years and analyzed the correlation between clinical outcome and potential predictors. Results: All patients had received at least one systemic therapy for metastatic disease before referral. Only two patients declined phase I trial therapy. The median progression-free (PFS) and overall (OS) survivals were 3.6 and 10.6 months, respectively. Patients harboring phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) mutations or phosphatase and tensin homolog loss, and those with more than two sites of metastasis who received more than one prior systemic chemotherapy before the referral had median PFS of 6.7 and 1.8 months, and median OS of 12.6 and 2.9 months, respectively. Conclusion: Patients with more than two metastatic sites who had received more than one prior system therapy had dismal outcomes. An aberrant PI3K pathway was frequently identified and associated with favorable outcome, providing a promising target.*

Cervical cancer is a common gynecological malignancy and cause of cancer-related death worldwide (1). In 2013, an estimated 12,340 patients were diagnosed, and 4,030 died, of the disease in the United States (2). Pathologically, squamous cell carcinoma and adenocarcinoma account for 95% of cervical cancer (3). Fortunately, most patients are diagnosed with disease at an early stage and have a high rate of long-term survival after they have received well-established curative therapy (4). Patients who present with metastatic cervical cancer not amenable to radical local excision or curative radiation therapy have a poor prognosis (5, 6). Platinum-based chemotherapy regimens are the first-line standard-of-care but provides a median progression-free survival (PFS) of 5.8 months and a median overall survival (OS) of 12.9 months (6, 7). Patients in whom first-line systemic therapy fails have a particularly poor outcome, with a median OS of approximately 7 months (8, 9). Subsequent therapies using conventional systemic chemotherapeutic regimens increase toxicity without providing a meaningful clinical benefit (8). The poor prognosis of these patients necessitates the development of novel therapeutic regimens (10, 11). To explore potential directions of future drug development for the treatment of patients with advanced cervical cancer, we conducted a retrospective study to analyze characteristics and major clinical outcomes for such patients with metastatic cervical cancer who were referred to a phase I trial clinic at The University of Texas MD Anderson Cancer Center (MD Anderson).

Patients and Methods

Patient selection. All consecutive patients with metastatic cervical cancer who were referred to the Department of Investigational Cancer Therapeutics (Phase I Clinical Trials Program) at MD Anderson from January 1, 2006, to June 30, 2012, were included in this retrospective chart-review study. Follow-up is defined as the time from the initial visit to the phase I clinic until the date of death or the last visit before January 14, 2013. This study was approved by the MD Anderson Institutional Review Board, PA13-0627.

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Key Words: Cervical cancer, phase I trial, *PIK3CA* mutation, *PTEN* loss, outcome analysis.

Data collection. Two individuals independently abstracted data from patients' electronic medical records and then cross-checked the collected data. Any disagreement between them or uncertainty was brought to a joint chart review with the corresponding author to reach an agreement. Clinical information abstracted included age, ethnicity/race, residence, the date of the initial diagnosis and staging, prior treatment for metastatic disease (systemic chemotherapy, radiation, chemoradiation, or surgery), the date of the initial phase I clinic visit, baseline Eastern Cooperative Oncology Group (ECOG) performance status, baseline serum albumin and serum lactate dehydrogenase, the number of sites of metastases, tumor histology, tumor mutation status, phase I clinical trial therapy, and major clinical outcomes (toxicity, objective response, and survival). The data were entered into a Microsoft Excel data sheet for further statistical analyses as described below. Patients had been enrolled into phase I trials on the basis of trial availability, clinical judgment of their referring physicians and phase I clinic physicians, and their meeting trial eligibility criteria. If a patient did not respond to one phase I trial therapy, they were considered for another available phase I trial if eligible and willing to participate.

Toxicity and objective responses in the various phase I trials were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 or v4.0 (http://ctep.cancer.gov/reporting/ctc.html) (12) and the Response Evaluation Criteria in Solid Tumors version 1.0 or 1.1 (13, 14), respectively. PFS was defined as the time from the date of initial treatment to the date of the first objectively documented tumor progression, death, or most recent follow-up. OS was defined as the time from the initial phase I clinic visit to death or most recent follow-up.

Statistical analyses. Categorical data were described using contingency tables. Continuously scaled measures were summarized with descriptive statistical measures (*i.e.* median with range). PFS and OS rates were estimated using the Kaplan–Meier method. Patients still alive at the last follow-up were censored at that time. Univariate and multivariate Cox proportional hazards models were fit to assess the association between PFS, OS and potential risk factors such as age, ethnicity, histology, the number of prior systemic chemotherapies, prior radiotherapy, prior surgery, baseline Eastern Cooperative Oncology Group (ECOG) performance status, the number of metastatic sites, baseline serum lactate dehydrogenase, and baseline serum albumin. Statistical inferences were based on two-sided tests at a significance level of $p<0.05$. Statistical analyses were carried out using SPSS version 19 (SPSS Inc., Chicago, IL, USA).

Results

Patients. All 54 consecutive patients with metastatic cervical cancer were referred from the Gynecological Oncology Center at MD Anderson. These patients were followed-up from their initial phase I clinic visit until death or the last follow-up before January 14, 2013. Patient characteristics are summarized in Table I. All patients had received at least one regimen of systemic chemotherapy before referral. Ninety-six percent (52/54), 27% (14/52), 29% (4/14), and 25% (1/4) of the patients were enrolled into a first, second, third, and fourth phase I trial, respectively.

Among 36 patients who underwent molecular marker studies in a Clinical Laboratory Improvement Amendments-certified molecular diagnostic laboratory, 9 out of 34 tested patients (26%) had phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit-alpha (*PIK3CA*) mutations and 12 out of 19 tested patients (63%) had phosphatase and tensin homolog (*PTEN*) loss. The presence of *PIK3CA* mutations or *PTEN* loss was not significantly associated with the histological diagnosis. Other mutations detected in this cohort of patients with metastatic cervical cancer included Kirsten rat sarcoma viral oncogene homolog (*KRAS*; 1/28, 3.6%), neuroblastoma RAS viral (v-ras) oncogene homolog (*NRAS*; 1/15, 6.7%), and epidermal growth factor receptor (*EGFR*; 1/21, 4.8%). No mutation was identified in v-raf murine sarcoma viral oncogene homolog B (*BRAF*; 0/24), v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (*c-KIT*; 0/12), or met proto-oncogene (*MET*; 0/9).

Toxicity evaluation. Fifty-two patients were included in the toxicity evaluation; the other two patients declined phase I trial therapy at the phase I clinic. These patients received a total of 365 cycles of therapy in 39 phase I trials. During their first phase I trials, 42% of patients (22/52) experienced 32 episodes of grade 3 or higher toxicity: neutropenia or urinary tract infection (5 each, 16%); thrombocytopenia (4, 13%); intractable nausea/vomiting (3, 9%); renal function impairment, pain, or pneumonia (2 each, 6%); and neutropenic fever, anemia, septic shock, hypokalemia, hypophosphatemia, bacterial infection, aspartate transaminase elevation, bowel perforation, or acute coronary syndrome (1 each, 3%). During their second phase I trials, 14% of patients (2/14) developed grade 3 or higher toxicity: hypertension, or fatigue (1 each, 7%). No grade 3 or higher toxicity was observed in the 4 patients who had tumor progression within the initial 8 weeks of therapy.

Responses and PFS. Fifty-two patients were included in the response analysis; the other 2 patients declined phase I trial therapy after the initial phase I clinic visit. In their first phase I trials, the patients had one complete remission (CR) and six partial responses (PRs); 10 had stable disease (SD) of six months or more. The rate of CR/PR/SD≥6 months was 33% (17/52). The median PFS for first trials was 3.6 months [95% confidence interval (CI)=2.3-4.9 months]. In their second phase I trials, the patients had a rate of 29% PR/SD≥6 months (4/14; 1 PR and 3 SD) and a median PFS of 4.7 months (95% CI=0-9.5 months). In their third (n=4) and fourth (n=1) phase I trials, no CR, PR, or SD was observed. Univariate and multivariate analyses revealed that median PFS was shorter in patients who had received more than one prior systemic chemotherapy regimen and in those who had more than two metastatic sites, as shown in Table II. We then

Table I. *Baseline patient and disease characteristics (n=54).*

Characteristic		Number of patients (%)
Age, years	Median (range)	47 (22-73) years
Race/ethnicity	White	34 (63)
	African American	7 (13)
	Hispanic	9 (17)
	Other	4 (7)
Residence in Texas	Yes	37 (69)
Pathology	Squamous cell carcinoma	33 (60)
	Adenocarcinoma	15 (28)
	Adenosquamous cell carcinoma	3 (6)
	Small cell carcinoma	2 (4)
	Melanoma	1 (2)
FIGO stage at initial diagnosis	I	16 (30)
	II	11 (20)
	III	11 (20)
	IV	16 (30)
Prior therapy for metastatic disease	Surgery	23 (43)
	Radiotherapy	41 (76)
	Systemic chemotherapy	54 (100)
ECOG performance status	0	12 (22)
	1	33 (61)
	2	8 (15)
	3	1 (2)
Metastatic sites	≤2	36 (67)
	>2	18 (33)
Serum lactate dehydrogenase	≤618 IU/l	46 (85)
	>618 IU/l	8 (15)
Serum albumin	≥3.5 g/dl	45 (83)
	<3.5 g/dl	9 (17)

ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics.

stratified the 52 patients into three groups according to whether they had 0, 1, or 2 of these two risk factors. In their first phase I trials, the groups with 0, 1, and 2 risk factors had a median PFS of 6.4 months (N=20; 95% CI=3.0-9.8 months), 2.5 months (N=24; 95% CI =1.7-3.4 months), and 1.4 months (N=8; 95% CI=0.6-2.3 months) months, respectively (p=0.03).

We also examined PFS by tumor mutation and toxicity. The first phase I trials resulted in a 61% rate of PR/SD ≥6 months (11/18: 4 PRs and 7 SD ≥6 months) and a median PFS of 6.7 months (95% CI=5.5-7.9 months) in patients with *PIK3CA* mutations or *PTEN* loss; these compared favorably to the 25% rate of CR/PR/SD ≥6 months (4/16: 1 CR, 2 PRs, and 1 SD ≥6months; p=0.045) and median PFS of 2.9 months (95% CI, 2.0-3.8 months; p=0.054) in patients without the *PIK3CA* mutations or *PTEN* loss (Figure 1a). The first phase I trials resulted in a 50% CR/PR/SD ≥6 months (N=11: 1 CR, 2 PRs, and 8 SD) and a median PFS of 6 months (95% CI=2.7-9.3 months) in 22 patients who experienced grade 3 or higher toxicities; this was significantly better than the 20% rate of PR/SD ≥6 months (N=6: 4 PRs and 2 SD ≥6 months; p=0.036) and median PFS of 2.3 months (95% CI=1.7-2.9 months; p=0.049) in 30 patients who did not experience grade 3 or higher toxicity (Figure 1b).

Overall survival. All 54 patients were included in the OS evaluation. The median OS from the initial phase I clinic visit was estimated to be 10.6 months (95% CI=7.7-13.5 months), while the median OS from the date when the patients were initially diagnosed as having metastatic diseases, was estimated to be 19.1 months (95% CI=12.7-25.4 months; Figure 1c). A multivariate analysis was performed to identify independent risk factors associated with reduced OS from initial phase I clinic visits (Table III). Among the 10 factors included, only two predicted a shorter OS: more than two metastatic sites at presentation to the phase I clinic (p=0.002) and more than one prior systemic chemotherapy regimen (p=0.014). When patients were stratified into three groups on the basis of number of independent risk factors (more than two metastatic sites and more than one prior systemic chemotherapy), the median OS

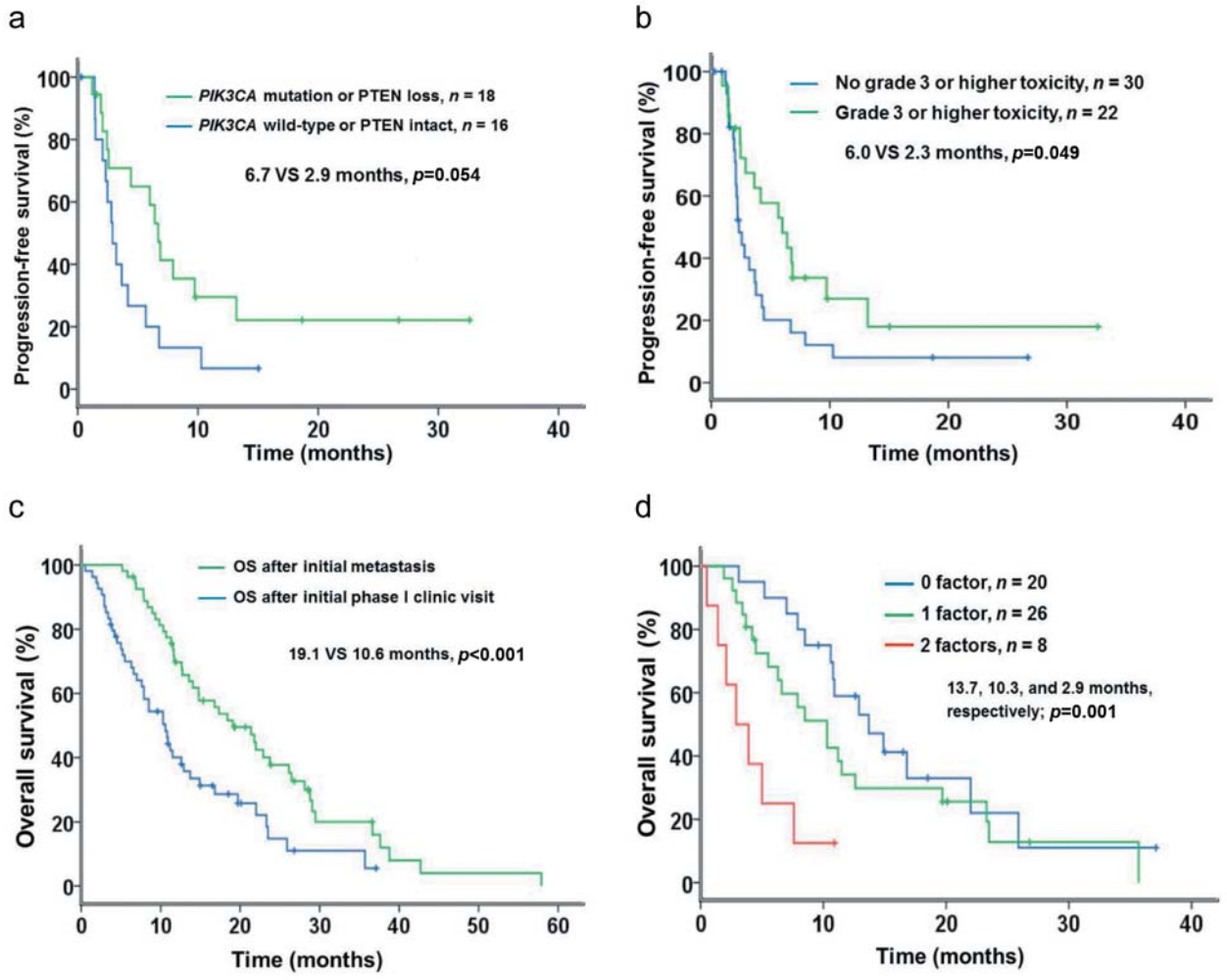

Figure 1. *Kaplan–Meier survival plots. a: Patients with phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit-alpha (PIK3CA) mutations or phosphatase and tensin homolog (PTEN) loss (in green) had a median progression-free survival (PFS) of 6.7 months (95% confidence interval (CI)=5.5-7.9 months), which compared favorably to that in patients with wild-type PIK3CA/intact PTEN (in blue; 2.9 months; 95% CI=2.0-3.8 months; p=0.054). b: Patients who had grade 3 or higher toxicities (in green) had a significantly longer PFS (6.0 months; 95% CI=2.7-9.3 months) than those who did not (in blue; 2.3 months; 95% CI=1.7-2.9 months; p=0.049). c: Patients had a median overall survival (OS) of 10.6 months (95% CI=7.7-13.5 months) from the initial phase I clinic visit (in blue) and 19.1 months (95% CI=12.7-25.4 months) from the initial diagnosis of metastasis (in green). d: OS for patients stratified by presence of 0 (blue), 1 (green), or 2 (red) risk factors (more than two metastatic sites and more than one prior systemic therapy): (p=0.001). The median OSs were 13.7 months (95% CI, 8.5-18.9 months), 10.3 months (95% CI=6.6-14.0 months), and 2.9 months (95% CI=0.4-5.4 months), respectively.*

was 13.7 months (N=26; 95% CI=8.5-18.9 months), 10.3 months (N=20; 95% CI=6.6-14.0 months), and 2.9 months (N=8; 95% CI=0.4-5.4 months) in patients with 0, 1, and 2 of the risk factors (p=0.001), respectively (Figure 1d).

Discussion

In this retrospective study, patients with metastatic cervical cancer appeared to have a survival benefit from participating in phase I trials: the median OS from the initial diagnosis of metastatic diseases was 19.1 months, which compares favorably to the reported 12.9 median OS of patients enrolled in phase III trials (6, 7, 15). This finding may alleviate some concerns of referring physicians and patients that the goals of phase I trials are merely to define the recommended drug dosage for phase II trials and to evaluate safety profiles and pharmacokinetic properties of the study regimens (16-18). In our multivariate analysis of predictors of PFS and OS, the only independent risk factors were number of metastatic sites and number of prior chemotherapy regimens. More than two

Table II. *Univariate and multivariate analyses of potential predictors of shorter progression-free survival (PFS) (n=52).*

Variable	Level	Number of patients	Median PFS (months)	95% CI	*p*-Value		Effect	Standard error	Hazard ratio
					Univariate	Multivariate			
Age	≤47	30	3.7	1.7-5.6	0.528	0.556	0.222	0.376	1.248
	>47	22	3.2	1.7-4.7					
Race	White	33	3.7	1.8-5.5	0.322	0.054	0.845	0.438	2.329
	Others	19	2.3	0.9-3.7					
Serum albumin	≥3.5 g/dL	44	3.2	1.7-4.7	0.204	0.074	0.86	0.482	2.362
	<3.5 g/dL	8	3.7	0.1-7.3					
Serum lactate dehydrogenase	≤618 IU/L	44	2.9	1.5-4.3	0.249	0.062	–1.04	0.557	0.354
	>618 IU/L	8	6.9	6.4-7.3					
Metastatic sites	≤2	34	4.3	1.8-6.7	0.086	0.005	1.167	0.412	3.212
	>2	18	2.1	1.6-2.7					
ECOG performance status	≤1	44	3.7	2.0-5.3	0.212	0.917	–0.053	0.506	0.949
	>1	8	2.6	1.6-3.5					
Histology	Squamous	32	3.6	1.6-5.7	0.733	0.561	–0.235	0.404	0.79
	Other	20	2.9	1.9-3.9					
Prior systemic chemotherapy	1 line	30	4.2	1.0-7.3	0.08	0.018	0.926	0.39	2.524
	>1 line	22	2.4	2.0-2.9					
Prior surgery	No	30	2.6	2.0-3.2	0.194	0.578	–0.2	0.361	0.818
	Yes	22	4.3	0-8.8					
Prior radiotherapy	No	13	3.7	0-8.1	0.596	0.916	0.044	0.418	1.045
	Yes	39	2.9	1.4-4.4					

ECOG: Eastern Cooperative Oncology Group, CI: confidence interval.

sites of metastasis and more than one chemotherapy regimen for metastatic disease before referral to the phase I clinic were associated with shorter median PFS and OS. Compared to the other risk factors from the Royal Marsden Hospital prognostic scoring system (high serum lactate dehydrogenase level and low serum albumin level, along with more than two metastatic sites) (19) and the MD Anderson prognostic scoring system (the three Royal Marsden Hospital risk factors plus ECOG performance status >1 and gastrointestinal cancer) (20) were not survival predictors in this cohort of patients. Stratifying patients by whether they had more than one prior systemic chemotherapy or more than two metastatic sites (0, 1, or 2 of these factors) resulted in three distinct groups for PFS and three for OS.

Patients with an aberrant PI3K pathway had a significantly better rate of clinical CR/PR/SD ≥6 months and a longer median PFS than patients without an aberrant PI3K pathway. In addition, patients who had grade 3 toxicities has higher rates of CR/PR/SD ≥6 months and a higher median PFS than patients without such toxicities. However, there was no significant difference in median OS in these two groups. Although patients with greater toxicities are likely to be those patients who received higher doses in phase I trials, the overall survival outcomes suggest that it might not be necessary to treat patients at dose levels that are toxic.

When considering the clinical relevance of our findings, several limitations should be borne in mind. Firstly, selection bias in patient referral to a phase I clinic and the availability of a phase I trial at the time of referral may limit the generalizability of our findings. Patients with poor outcomes may have been selectively excluded from being referred to a phase I trial. Therefore, the patients who were referred to our phase I clinic and included in this retrospective study may have better survival outcomes than patients who were not referred. Secondly, we had a limited sample size available for sub-group analyses, which confounded the ability to validate the statistical significance in category assessments. Thirdly, conclusions from this retrospective study require further validation by larger prospective studies. Finally, since 52 patients were treated in 39 phase I trials, it was not possible to link clinical benefits to any one specific regimen.

To our knowledge, this is the first retrospective study to summarize the clinical outcomes of patients with metastatic cervical cancers referred to a phase I clinic in a comprehensive cancer Center. Our results suggest a potential survival benefit from participating in a phase I trial. The presence of more than two metastatic sites in patients who had received more than one prior systemic therapy was associated with a very short PFS and OS; physicians should be aware of this when a patient with metastatic cervical

Table III. *Univariate and multivariate analyses of potential predictors of shorter overall survival (OS) (n=54).*

Potential risk factors	Level	Number of patients	Median OS (months)	95% CI	*p*-Value		Effect	Standard error	Hazard ratio
					Univariate	Multivariate			
Age	≤47 years	30	7.9	3.3-12.5	0.6	0.856	-0.062	0.342	0.94
	>47 years	24	12.6	8.9-16.3					
Race	White	34	8.5	3.8-13.2	0.993	0.686	0.172	0.425	1.188
	Other	20	10.9	9.7-12.1					
Serum albumin	≥3.5 g/dl	45	10.8	7.7-13.9	0.385	0.127	0.733	0.481	2.082
	<3.5 g/dl	9	7.9	4.0-11.8					
Serum lactate dehydrogenase	≤618 IU/l	46	10.3	7.3-13.3	0.747	0.737	0.174	0.519	1.19
	>618 IU/l	8	12.6	5.7-19.5					
Metastatic sites	≤2	36	11.2	8.4-14.0	0.044	0.002	1.141	0.374	3.131
	>2	18	5.5	2.8-8.2					
ECOG performance status	≤1	45	10.6	6.9-14.3	0.564	0.827	0.117	0.534	1.124
	>1	9	10.9	5.8-16.0					
Histology	Squamous	33	10.6	6.6-14.6	0.379	0.062	-0.67	0.358	0.512
	Other	21	12.6	4.1-21.1					
Prior systemic chemotherapy	1 line	30	12.6	9.0-16.2	0.077	0.014	0.892	0.363	2.439
	>1 line	24	6.6	2.1-11.1					
Prior surgery	No	31	8.5	5.7-11.3	0.807	0.502	0.232	0.346	1.262
	Yes	23	11.5	8.5-14.5					
Prior radiotherapy	No	13	12.6	5.6-19.6	0.904	0.514	0.284	0.436	1.329
	Yes	41	10.3	7.0-13.6					

ECOG: Eastern Cooperative Oncology Group, CI: confidence interval.

cancer is referred to a phase I clinic. Approximately 50% of patients who were tested for tumor mutation status had *PIK3CA* mutations or *PTEN* loss; these were associated with better response rates and longer PFS. These findings support previous findings that therapeutic regimens targeting the aberrant PI3K pathway are promising for the treatment of advanced cervical cancer (21-25).

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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Received January 21, 2014
Revised February 18, 2014
Accepted February 19, 2014