

# Potential impact of mTOR inhibitors on cervical squamous cell carcinoma: A systematic review

DANIELE XAVIER ASSAD<sup>1,2</sup>, SILVIA TAVEIRA ELIAS<sup>1</sup>, ANDRÉIA CRISTINA MELO<sup>3</sup>,  
CARLOS GIL FERREIRA<sup>3-5</sup>, GRAZIELA DE LUCA CANTO<sup>6,7</sup> and ELIETE NEVES SILVA GUERRA<sup>1</sup>

<sup>1</sup>Oral Histopathology Laboratory, School of Health Sciences, University of Brasília, Brasília, Federal District 70910-900;

<sup>2</sup>Oncology Center, Hospital Sírio-Libanês, Brasília, Federal District 71635-610; <sup>3</sup>Department of Clinical Research, National Institute of Cancer, Rio de Janeiro 20220-410; <sup>4</sup>National Clinical Cancer Research Network, Ministry of Health, Brasília, Federal District 70058-900; <sup>5</sup>Department of Clinical Research, D'or Institute for Research, Rio de Janeiro 22281-100;

<sup>6</sup>Department of Dentistry, Federal University of Santa Catarina, Florianópolis, Santa Catarina 88036-800, Brazil;

<sup>7</sup>Department of Dentistry, University of Alberta, Edmonton, AB T6G 1C9, Canada

Received September 16, 2015; Accepted May 10, 2016

DOI: 10.3892/ol.2016.5157

**Abstract.** The aim of the present systematic review was to analyze the potential impact of mammalian target of rapamycin (mTOR) inhibitors on the treatment of cervical squamous cell carcinoma (CSCC). A systematic literature search was conducted in PubMed, PMC, Scopus, Cochrane Library, LILACS, Web of Science, Google Scholar and ScienceDirect on January 19, 2015, without time and language restrictions. Studies that evaluated women of any age with CSCC and who received mTOR inhibitors alone or in association with other treatments were considered. Randomized and non-randomized clinical trials were included, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist was followed. Selected studies were methodologically appraised according to the Grades of Recommendation, Assessment, Development and Evaluation method to assess the quality of evidence. Of 642 identified citations, 43 studies were fully reviewed; however, only 3 studies met the inclusion criteria and were used for qualitative analysis. Of these, two studies were phase 1 and one was a phase 2 clinical trial. The studies included were not conclusive with regard to the association between mTOR inhibitor treatment and cervical cancer. The main analysis of secondary endpoints revealed that individuals treated with other drugs in association with mTOR inhibitors achieved partial responses (15.4-33.3%) or stable disease (17.6-28%). Treatment with mTOR inhibitors

in general was well tolerated in patients with metastatic disease. The predominant toxicities were grade 1 and 2. The phase 1 trials included in this review demonstrated that mTOR inhibitor treatments are feasible and safe. However, the currently available evidence is insufficient to determine the effect of mTOR inhibitors on CSCC, and further investigation in high-quality, randomized clinical trials is required.

## Introduction

Cervical cancer (CC) is a major public health concern, representing the fourth most commonly diagnosed cancer in women and the seventh overall, with an estimated 528,000 new cases worldwide in 2012 (1). Globally, ~266,000 mortalities from CC occurred in 2012, accounting for 7.5% of all female cancer mortalities; this number is expected to increase to 410,000 by the year 2030 (2).

Although the systemic treatment of cervical squamous cell carcinoma (CSCC) has advanced into an era of targeted drugs, such as erlotinib (3) and bevacizumab (4), the antitumor efficacies of current therapies are limited, most likely due to the high degree of cancer clonal heterogeneity, intratumoral genetic heterogeneity and cell signal complexity (5). In this context, there is an urgent necessity for more active treatment and rationally designed targeted therapies (6).

More than 95% of CSCC patients are positive for oncogenic human papillomavirus (HPV) DNA. HPV infection plays a central role in the development of this cancer, particularly infection with the high-risk subtypes, HPV 16 and 18 (7). The HPV infection has multiple intracellular effects in different signaling pathways. The phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway is often dysregulated in gynecological cancers, particularly in HPV-associated tumors (6). Alterations that cause the activation and dysregulation of the PI3K/AKT/mTOR pathway may act as potentially drug-treatable targets (8).

The PI3K/AKT/mTOR signaling pathway, which functions in mammal cells, acts to coordinate important cell

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*Correspondence to:* Dr Eliete Neves Da Silva Guerra, Oral Histopathology Laboratory, School of Health Sciences, University of Brasília, Campus Darcy Ribeiro, Superquadra Norte 205, Building H, 201 Asa Norte, Brasília, Federal District 70910-900, Brazil  
E-mail: elieteneves@unb.br

**Key words:** mammalian target of rapamycin inhibitors, cervical cancer, systematic review, evidence-based medicine

activities (6). Tumor cells may have a greater sensitivity to mTOR inhibitors than normal cells as a consequence of the dysregulation of mTOR and other proteins associated with this pathway in solid tumors (9). Mechanisms for pathway activation include loss of function of the tumor suppressor gene phosphatase and tensin homolog (*PTEN*), amplification or mutation of *PI3K*, amplification or mutation of *AKT*, activation of growth factor receptors and exposure to carcinogens (10,11).

Rapamycin was the first mTOR inhibitor to be defined; however, other analogs of rapamycin have been developed, including temsirolimus and everolimus (12). Certain natural compounds also possess mTOR inhibitor properties, such as curcumin, resveratrol and epigallocatechin gallate (13). Temsirolimus and everolimus have already been incorporated into clinical practice to treat kidney and breast cancer (14-16). Therefore the present systematic review was conducted to verify the potential effect of mTOR inhibitors on CSCC, and thereby provide support for future rationally designed strategies that may involve this pathway.

## Materials and methods

**Protocol and registration.** This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (17). The protocol was registered in PROSPERO (no. CRD42015016329) (18).

**Eligibility criteria.** Randomized and non-randomized clinical trials that evaluated women of any age with CSCC who received mTOR inhibitors alone or in association with other treatments (drugs or radiotherapy) were included.

Studies were excluded for the following reasons: i) Different target conditions, such as studies that did not use mTOR inhibitors to treat CSCC or did not verify the association between mTOR inhibitors and CSCC; ii) study assessed associations between mTOR inhibitor treatment and CSCC *in vitro* or *in vivo* in animal studies; iii) insufficient information provided regarding histological type, response or treatment.

**Information sources and search strategies.** Detailed individual search strategies were developed for each of the following bibliographic electronic databases: Cochrane Library (<http://www.cochranelibrary.com>), Google Scholar (<https://scholar.google.com.br>), LILACS (<http://lilacs.bvsalud.org>), PMC (<https://www.ncbi.nlm.nih.gov/pmc/>), PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/>), ScienceDirect (<http://www.sciencedirect.com>), Scopus (<https://www.scopus.com>) and Web of Science (<http://login.webofknowledge.com/>). The search strategy for Pubmed included the following terms: 'Cervical cancer' or 'uterine cancer' or 'cervix cancer' or 'cervical neoplasm' or 'cervix neoplasm'; and 'mTOR'. The reference lists in the selected articles were also searched to identify any additional references that may have been missed in the electronic databases searches. The search was conducted through January 19th, 2015, across all databases, without date and language restrictions. The references were managed and the duplicates removed using appropriate software (EndNote; Thomson Reuters, New York, NY, USA).

**Study selection.** Studies were considered for inclusion in two phases. In the first phase, two reviewers (D.X.A. and S.T.E.) independently reviewed the titles and abstracts of all references. These authors selected articles that met the inclusion criteria based on their titles and abstracts. In the second phase, the two authors read the full text of all selected articles and excluded studies that did not meet the inclusion criteria. The same two authors independently reviewed all full text articles. Disagreements were resolved by consensus of the authors or by a third reviewer (E.N.S.G.).

**Data collection process and data items.** One reviewer (D.X.A.) collected the required information from the selected articles, including the following: Author, year, country, study design, treatment agents, number of patients with CC and CSCC included, patient population with number of prior treatments, maximum tolerated dose (MTD) of treatment, recommended dose of treatment (RD), number of partial responses (PRs), percentage of patients with stable disease (SD) lasting  $\leq 6$  months, time to treatment failure (TTF) or duration of progression-free survival (PFS), complications, main conclusions and clinical application. A second reviewer (S.T.E.) crosschecked all retrieved information. Disagreements were resolved by author consensus or by a third reviewer (E.N.S.G.).

**Risk of bias in individual studies.** The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach was used to assess the quality of evidence (19). Two authors (D.X.A. and S.T.E.) completed the required criteria necessary to qualify the selected articles, which were categorized as 'high', 'moderate', 'low' or 'very low', according to the analysis of each study. The third reviewer (E.N.S.G.) was involved when required to make a final decision.

**Summary measures.** Any reported outcome or efficacy measurements were considered, including MTD, RD, response rate (RR), percentage of patients with SD lasting  $\geq 6$  months, PFS time, TTF and complications.

**Synthesis of results.** A meta-analysis was planned since the data from the included studies was considered relatively homogeneous.

## Results

**Study selection.** In the first phase of study selection, 642 citations were identified across the seven electronic databases and Google Scholar. Following the removal of duplicates, 514 citations remained. Comprehensive evaluation of the title and abstracts was completed and 472 articles were excluded; thus, 42 articles remained after the first phase. One additional study was included from the reference lists of the identified studies. From the 43 articles retrieved, full text reviews were conducted. This process excluded 40 studies (20-59). Finally, 3 studies were selected (60-62). A flow chart detailing the process of identification, inclusion and exclusion of studies is shown in Fig. 1.

**Study characteristics.** The selected studies were conducted in two countries: The USA (60,61) and Canada (62). All 3 studies

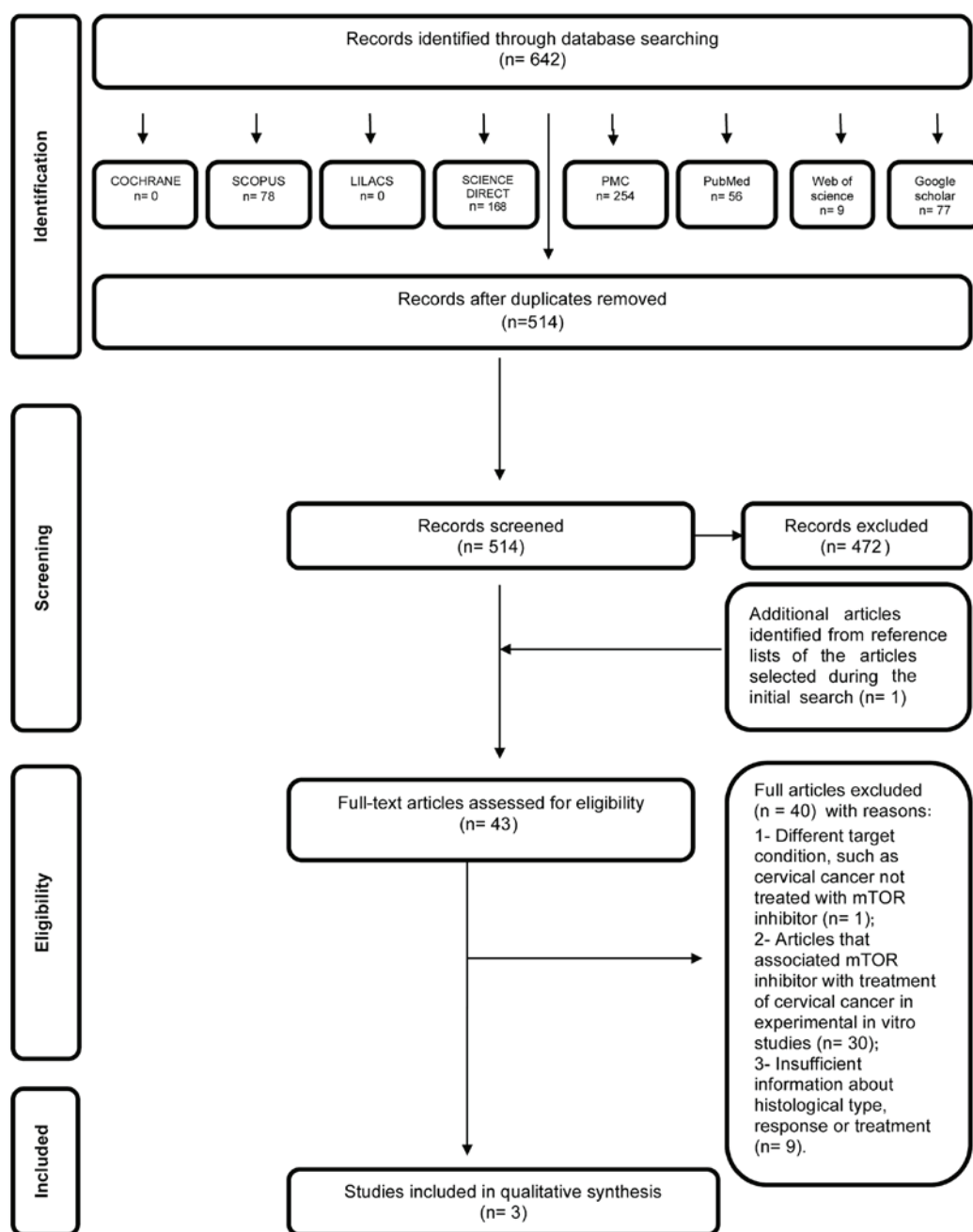


Figure 1. Flow diagram of literature search and selection criteria adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (17).

were published recently, in 2011 (60), 2013 (62), 2014 (61), and all were written in English. All included articles were non-randomized clinical trials; two studies were phase 1 and one was phase 2. A summary of the descriptive characteristics of the included studies is given in Table I.

**Risk of bias within studies.** The GRADE approach (19) was used to assess the quality of evidence of the included studies, as outlined in Table II. All studies were categorized as having a low quality level of evidence (60-62). All had serious issues with regard to the design, none had control groups, and all lacked blinding. Imprecision occurred in one study due to the extremely small number of patients included (61).

The clinical application of the studies was also evaluated. The mTOR inhibitor application in CC was classified

as 1 (potential effect in CSCC treatment), 2 (inconclusive or 3 (evidence not supportive of mTOR inhibitors a drug for CSCC treatment). A summary of descriptive characteristics of the studies is given in Table I. All studies were classified as inconclusive with regard to the effect of mTOR inhibitors in CSCC (Table I).

#### Synthesis of results

**Study 1.** The study by Moroney *et al* (60) evaluated 74 patients with gynecological and breast malignancies who were treated with liposomal doxorubicin, bevacizumab and temsirolimus. This included 13 CC patients, of whom 10 had CSCC. The study was a non-randomized, phase 1 clinical trial, for which the primary endpoints were to establish the MTD and characterize dose-limiting toxicities. Secondary endpoints included

Table I. Summary of descriptive characteristics of clinical studies in included studies.

Author, year (ref.), country	Study design	Treatment agents	No. of patients with CC/CSCC	Patient population	MTD	RD	PR, n (%) <sup>a</sup>	SD ≥6 months	TTF or PFS	Complications	Main conclusions	Clin. app. <sup>b</sup>
Moroney <i>et al</i> , 2011 (60), USA	Phase 1, NR	Liposomal doxorubicin, bevacizumab and temsirolimus	13 CC/ 10 CSCC	Metastatic disease; median prior 4 prior regimens	Level 6: Bevacizumab, 15 mg/kg, d1; liposomal doxorubicin, 20-30 mg/ m <sup>2</sup> , d1; and temsirolimus, 25 mg IV, d1, 8 and 15	Bevacizumab, 15 mg/kg, d1; liposomal doxorubicin, 20-30 mg/ m <sup>2</sup> , d1; and temsirolimus, 25 mg IV, d1, 8 and 15	2 among CSCC patients (15.4%)	17.6% (among all patients)	112 days (among all patients) <sup>b</sup> ; 172 days (among patients with PR) <sup>b</sup>	Grade 3 and 4 toxicities: Thrombocytopenia (9.5%), mucositis (6.7%), cardiac (4.1%), genitourinary (1.4%), bowel perforation (2.7%)	Combination is well tolerated with manageable side effects; 2 PRs among 13 CC patients	2
Piha-Paul <i>et al</i> , 2014 (61), USA	Phase 1, NR	Bevacizumab and temsirolimus	6 CC/ 4 CSCC	Metastatic disease; median prior 4 prior regimens	Dose level 13: Temsirrolimus, 25 mg IV, d1, 8 and 15; bevacizumab, 15 mg/kg IV was reached and no MTD was obtained	N/A	2 among CSCC patients (33.3%)	20% (among all patients)	N/A	Grade 3 and 4 toxicities: Thrombocytopenia (10%), mucositis (2%), hypertension (2%), hypercholesterolemia (2%), fatigue (7%), increased AST (2%), neutropenia (2%)	Bevacizumab and temsirolimus were well tolerated; 2 PRs among 6 CC patients	2

Table I. Continued.

Author, year (ref.), country	Study design	Treatment agents	No. of patients with CC/CSCC	Patient population	MTD	RD	PR, n (%) <sup>a</sup>	SD ≥6 months	TTF or PFS	Complications	Main conclusions	Clin. app. <sup>b</sup>
Tinker <i>et al</i> , 2013 (62), Canada	Phase 2, NR	Temsirolimus	38 CC/ 22 CSCC	Metastatic disease; ≤1 prior therapy permitted	N/A	N/A	0	28% (95% confidence interval, 14-43%) among all patients	3.52 months (among all patients)	Grade 3 toxicity: fatigue (5.4%), mucositis (5.4%), rash (2.7%), lymphopenia (43.2%), anemia (16.2%), leucopenia (2.7%), hyponatremia (16.2%), hypertriglyceridemia (5.4%), hypokalemia (10.8%)	Temsirolimus was not active in this population as defined by RECIST. SD rates were notably high.	3

<sup>a</sup>Data not available in the original article; the authors calculated data from information available in the article (organ specific histological subtypes grouped to determine denominator). <sup>b</sup>Clinical application of mTOR inhibitors was classified as follows: 1, potential effect in cervical cancer treatment; 2, inconclusive; and 3, evidence not supportive as a drug for CSCC treatment. CC, cervical cancer; CSCC, cervical squamous cell carcinoma; MTD, maximum tolerated dose; RD, recommended dose; PR, partial response; SD ≥6 months, stable disease lasting ≥6 months; TTF, time to treatment failure; PFS, progression-free survival; NR, non-randomized; N/A, not available; d, day; IV, intravenously; AST, aspartate aminotransferase; RECIST, Response Criteria in Solid Tumors version 1.1.



Table II. Assessment of the quality of evidence for intervention.

Author, year (ref.)	Study design	Limitations in study design and/or execution <sup>a</sup>	GRADE factors					Overall quality
			Inconsistency	Indirectness	Imprecision	Publication bias	Moderate/large effect size	
Moroney <i>et al</i> , 2011 (27)	Phase 1, non-randomized	P	N	N	N	N	Not present	++
Piha-Paul <i>et al</i> , 2014 (28)	Phase 1, non-randomized	P	N	N	P (very few patients were included)	N	Not present	+
Tinker <i>et al</i> , 2013 (29)	Phase 2, non-randomized	P	N	N	N	N	Not present	++

<sup>a</sup>None of the included clinical trials had control groups, all lacked blinding and all were non-randomized. For GRADE factors (19): N, no serious limitations; P, presence of serious limitation. For overall quality (of evidence): +, very low; ++, low; +++ moderate; ++++, high.

a preliminary assessment of antitumor efficacy. All 74 patients were heavily pretreated with a median of 4 previous lines of chemotherapy. There were two PRs in the group of patients with CSCC [treated with dose level 6: Bevacizumab, 15 mg/kg intravenously (IV), day 1; liposomal doxorubicin, 30 mg/m<sup>2</sup> IV, day 1; and temsirolimus, 25 mg IV, days 1, 8 and 15]. The MTD for the study was reached at level 6. The RD for the corresponding phase 2 clinical trial study was as follows: Bevacizumab, 15 mg/kg, day 1; liposomal doxorubicin, 20-30 mg/m<sup>2</sup>, day 1; and temsirolimus, 25 mg IV, days 1, 8 and 15. The overall RR in this heavily pretreated population was 20.3%. Among all 74 patients included, 17.6% had SD lasting ≥6 months. The TTFs were 112 days [95% confidence interval (CI), 89-147 days] among all patients, and 172 among patients with PRs. The median overall survival (OS) time was 214 days (95% CI, 185-312 days).

All 74 patients (100%) experienced ≥1 adverse event that was at least possibly drug-related. These events were predominantly grades 1 or 2 and reversible. The treatment combination was relatively safe and well tolerated. Among the 15 responders (complete response plus PR), PI3K catalytic subunit α (*PIK3CA*) and *PTEN* statuses were known in 9 (60%) and 5 (33.3%), respectively. Of the 9 responders for whom *PIK3CA* mutational status was known, 4 (44.4%) were positive. Of the 5 responders for whom *PTEN* status was known, 3 (60%) were found to have *PTEN* loss. The tumor molecular analysis is listed in Table III. As the molecular alterations were not reported for each type of cancer separately, it is not possible to conclude anything regarding treatment responses and mutations in CSCC.

*Study 2.* Piha-Paul *et al* (61) evaluated 41 patients with advanced gynecological malignancies who were treated with bevacizumab and temsirolimus. There were 6 patients with CC included, of whom 4 had CSCC. This study was a non-randomized, phase 1 clinical trial. The primary endpoints were to establish the MTD and to characterize dose-limiting toxicities. Secondary endpoints included a preliminary assessment of antitumor efficacy. All patients were heavily pretreated with a median of 4 previous lines of chemotherapy. Among all patients included, 20% had SD lasting ≥6 months. Analysis of the mutational statuses of *PTEN*, *PIK3CA*, *RAS* and *RAF* was not performed for all included patients. Of the 2 patients who achieved PRs, the mutational status was not determined in 1, while the other patient was negative for *PIK3CA*, *RAS* and *RAF* mutations. The 5 responders for whom *PTEN* status was known were found to have *PTEN* loss. Tumor molecular analysis is listed in Table III. As the molecular alterations were not reported for each type of cancer, conclusions regarding the association of responses and mutations in CSCC are not possible.

Grade 1 and 2 toxicities were described in 71% of the patients. The highest dose escalation was obtained (dose level 13: Bevacizumab, 15 mg/kg IV, day 1; and temsirolimus, 25 mg/kg IV, days 1, 8 and 15), and the MTD was not reached. All 41 patients experienced ≥1 adverse event that was possibly drug-related. These events were predominantly grades 1 or 2 and reversible.

*Study 3.* Tinker *et al* (62) evaluated 38 patients with CC, of whom 22 had CSCC. The study was a non-randomized, phase 2 clinical trial. The primary endpoint was the objective

Table III. Tumor molecular analysis of the included studies.

Variable	Moroney <i>et al</i> (60)		Piha-Paul <i>et al</i> (61)		Tinker <i>et al</i> (62)	
	n (%)	Response comments	n (%)	Response comments	n (%)	Response comments
Total patients included	74	N/A	41	N/A	38	N/A
<i>KRAS</i> mutation status						
Number tested	49	N/A	17	N/A	0	N/A
Number with mutation	8 (16.3%)	8 <i>KRAS</i> mutation-positive patients (100%) achieved a response	1 (5.9%)	<i>KRAS</i> mutation-positive patient did not achieve SD $\geq 6$ months/PR	N/A	<i>KRAS</i> mutation was not tested
<i>NRAS</i> mutation status						
Number tested	0	N/A	17	N/A	0	N/A
Number with mutation	N/A	<i>NRAS</i> mutation was not tested	1 (5.9%)	<i>NRAS</i> mutation-positive patient did not achieve SD $\geq 6$ months/PR	N/A	<i>NRAS</i> mutation was not tested
<i>PIK3CA</i> mutation status						
Number tested	57	N/A	25	N/A	33	N/A
Number with mutation	16 (28.1%)	4 <i>PIK3CA</i> mutation-positive patients (25%) achieved a response	1 (4.0%)	The <i>PIK3CA</i> mutation-positive patient achieved a PR	8 (24.2%) <sup>a</sup>	The single patient with PR did not have <i>PIK3CA</i> mutation
<i>PTEN</i> status						
Number tested	25	N/A	2	N/A	33	N/A
Number with loss	11 (44.0%)	5 <i>PTEN</i> loss-positive patients (45.5%) achieved a response	0 (0.0%)	No <i>PTEN</i> loss was detected	3 (9.1%) <sup>a</sup>	The single patient with PR did not have <i>PTEN</i> loss

<sup>a</sup>Data not available in the original article; the authors calculated data from information available in the article. N/A, not applicable; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *NRAS*, neuroblastoma RAS viral oncogene homolog; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit  $\alpha$ ; *PTEN*, phosphatase and tensin homolog; PR, partial response; SD, stable disease.

RR, as determined by Response Evaluation Criteria in Solid Tumors (version 1.1). Up to 1 prior line of chemotherapy for metastatic or recurrent disease was permitted. Patients were treated with temsirolimus (25 mg IV, weekly) in 4-week cycles. Only 1 PR occurred, and this patient had cervical adenocarcinoma. The median duration of SD was 6.5 months (range, 2.4-12.0 months) and the proportion of patients with SD lasting  $\geq 6$  months was 28% (95% CI, 14-43%). The median PFS time was 3.52 months (95% CI, 1.81-4.7 months). There were 11 serious adverse events among 7 patients that were possibly related to the therapy protocol. Original diagnostic material was available for molecular analysis of 33 patients. No significant association was found between any of the markers and response to temsirolimus therapy. The 5 responders for whom *PTEN* status was known had *PTEN* loss. Tumor molecular analysis is presented in Table III.

**Risk of bias across studies.** The selected studies used similar methods, which reduced the possibility of misinterpretation.

The studies selected for this analysis were considered to be relatively homogeneous; however, they did not provide compatible data that would allow a meta-analysis.

## Discussion

The present study reviewed the available evidence regarding the potential impact of mTOR inhibitors in the treatment of CSCC. Palliation with platinum-based chemotherapy remains the standard of care for inoperable patients who have advanced disease (63). Few advances in medical management have occurred in recent years in the treatment of advanced recurrent gynecological malignancies, and a poor prognosis remains (12). Rationally designed molecularly targeted therapy is an emerging and important option in this setting (12).

mTOR is a serine/threonine protein kinase of the PI3K/AKT signaling pathway, with a critical role in controlling cancer cell growth, metabolism and cell cycle progression. Aberrant

PI3K-dependent signaling occurs frequently in a wide range of tumor types, including ovarian, endometrial and cervical cancers (6,12).

HPV infection of the uterine cervix is linked to the pathogenesis of CC. Preclinical *in vitro* and *in vivo* studies using HPV-containing human cervical carcinoma cell lines have demonstrated that rapamycin is able to induce growth delay of xenografts. Activation of Akt and mTOR in C5CC, and expression of phosphorylated mTOR have been reported to serve as markers to predict response to chemotherapy and survival of CC patients (8).

Several studies have provided evidence of the association between the activated PI3K/AKT/mTOR pathway and CC (8,12,64,65); however, few studies have analyzed the effect of treatment with mTOR inhibitors in CC patients (26,33-36, 44,46,47,53,60-62). Research has also been conducted in the field of combined treatment with mTOR inhibitors, chemotherapy and radiotherapy for locally advanced CC (66).

The present review identified only two phase 1 (60,61) and one phase 2 (62) clinical trials that met the inclusion criteria. All studies were non-randomized and included treatment with temsirolimus as the mTOR inhibitor agent. No control groups were included. The toxicities were manageable, and the predominant grade 3 and 4 toxicities included hematological and hepatic side effects.

The analysis of responses in these three studies was compromised due to the design of the studies and the lack of control groups. The two phase 1 studies had RR as secondary endpoints, and were thus not powered to detect differences in response. These studies revealed that a number of patients treated with chemotherapy or bevacizumab in association with mTOR inhibitors achieved PRs (15.4-33.3% of cases) or SD lasting  $\geq 6$  months (17.6-28% of cases). Patients were heavily pretreated in two studies (60,61), thus it is possible that RRs could be improved with these agents if used in earlier lines of treatment.

One serious limitation in determining the activity of temsirolimus in these two phase 1 studies, aside from the lack of statistical power to analyze RR, is the lack of a control arm. In the 22 C5CC patients included in the phase 2 study, there was no PR following treatment, only SD, and this study also did not include a control arm (62). The two phase 1 studies used temsirolimus combined with bevacizumab. Therefore, it cannot be affirmed whether the benefit obtained was due to the mTOR inhibitor, the combination of agents, or bevacizumab alone. In the study by Moroney *et al* (60), liposomal doxorubicin was also included, making this analysis further complicated. The other important limitation is that only the phase 2 trial included  $>20$  C5CC patients, but this study reported no responses to temsirolimus in C5CC patients (62). The phase 1 studies included  $\leq 10$  C5CC patients (60,61). Thus, it is not possible to conclude the effectiveness of temsirolimus in the treatment of C5CC based on the phase 1 studies, and the phase 2 study indicates that treatment is inactive.

There is evidence that tumor *PIK3CA* mutation status may predict response to PI3K/AKT/mTOR inhibitors (34). Only the study by Tinker *et al* (62) could be used to evaluate molecular alterations and responses, as the studies by Piha-Paul *et al* (61) and Moroney *et al* (60) did not report the results of molecular analysis in a separate manner with regard to the different types

of tumor. No established association between PI3K pathway activating mutations, loss of *PTEN* and treatment response could be determined in the study by Tinker *et al* (62).

In another study, Moroney *et al* (67) at the MD Anderson Cancer Center (University of Texas, Houston, TX, USA) described their experience of treatment with mTOR inhibitors in a phase 1 clinical trials of solid tumors (67). Patients with *PIK3CA* mutations were treated, whenever possible, with agents targeting the PI3K/AKT/mTOR pathway (36). In patients with C5CC, the presence of *PIK3CA* mutations was associated with a significantly longer OS time (median, 9.4 months) than the absence of *PIK3CA* mutations (median, 4.2 months;  $P=0.019$ ). Identifying patients who may, or more importantly may not, benefit from a molecularly targeted agent is highly desirable. Furthermore, evaluation of PI3K/AKT/mTOR pathway-targeted therapy is warranted, particularly in metastatic or recurrent C5CC (33).

The study of genomic and molecular characteristics of cervical tumors is underway by The Cancer Genome Atlas (TCGA; <http://cancergenome.nih.gov/cancersselected>). This will confirm the genomic and molecular alterations in the disease and provide rationale for specific targeted therapies. The evaluation of the PI3K/AKT/mTOR pathway by the TCGA is of great importance, as new classes of drugs targeted to this pathway are in the process of development, including PI3K inhibitors.

In summary, the current study is the first systematic review of the potential impact of mTOR inhibitors on C5CC treatment. Some serious methodological limitations of this review should be considered, such as that the studies were non-randomized, had only one arm, included a limited number of patients and lacked a control group. All studies were categorized as having a low or very low quality level of evidence. The currently available evidence is inconclusive with regard to the effects of mTOR inhibitors on C5CC. The phase 2 study in women with recurrent, unresectable, locally advanced or metastatic carcinoma of the cervix indicated that temsirolimus was inactive in this population. Investigation of PI3K/AKT/mTOR pathway-targeted therapies is warranted, and future studies should include information regarding mutations. Randomized, high-quality clinical trials are necessary to confirm the efficacy of mTOR inhibitors in the treatment of C5CC patients.

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