



Antitumor activity and safety of sirolimus for solid tumors with PIK3CA mutations: A multicenter, open-label, prospective single-arm study (KM 02-01, KCSG UN17-16)

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Background: PIK3CA contributes to cell growth via the PI3K-AKT-mammalian target of rapamycin (mTOR) signaling pathway. Mutations in the pathway are frequently observed in solid tumors. We assessed the efficacy and safety of sirolimus, an mTOR inhibitor, in chemotherapy-refractory solid tumors with PIK3CA mutations or amplifications.

Methods: This was an open-label, single-arm, multicenter pilot study. Twenty-four patients with solid tumors harboring a PIK3CA mutation were treated with sirolimus between July 2017 and March 2019. Treatment was continued until disease progression, unacceptable adverse events, or death. The primary end points were the overall response rate (ORR), disease control rate (DCR), and safety.

Results: The median follow-up time was 6.1 months. Two patients with rapid disease progression-related death, one who withdrew, and one with a non-target lesion only were excluded from the analysis. Among 20 evaluable patients, 6 patients showed stable disease and 14 showed progressive disease (ORR 0%, DCR 30%). The median progression-free survival was 2.39 months (95% confidence interval, 1.97–2.81 months). The most common adverse event was abdominal pain (20.8%), followed by anemia (16.7%) and fatigue (16.7%). The adverse events were generally manageable.

Conclusions: Although safe, sirolimus monotherapy did not show meaningful antitumor activity in chemotherapy-refractory solid tumors with PIK3CA mutations. Combinations of mTOR inhibitors for stabilization and other antitumor agents with beneficial effects on tumor volume may improve outcomes.

Keywords: PIK3CA mutation; mammalian target of rapamycin inhibitor (mTOR inhibitor); sirolimus

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Introduction

Phosphatidylinositol-4,5-bisphosphate 3-kinase (PIK) has important roles in cell growth and survival via the phosphatidylinositide 3-kinase (PI3K)-AKT serine/threonine kinase (AKT)-mammalian target of rapamycin kinase (mTOR) signaling cascades (1). Mutations in PIK3 catalytic subunit- α (*PIK3CA*), most frequently observed in the exon 9 helical domain (E542K and E545K) or exon 20 kinase domain (H1047R), can activate key proliferation signals in downstream pathways and contribute to tumor proliferation and survival (2-4). *PIK3CA* mutations or amplifications are frequently observed (14-36%) (5-8) and contribute to resistance to antitumor agents in solid tumors, such as cisplatin resistance in cervical cancer (9), HER2 resistance in breast cancer (10,11), or cetuximab resistance in colorectal cancer (12).

Numerous drugs targeting the PIK3-AKT-mTOR pathway have been developed (13-17). The first-generation inhibitors of this pathway were mTOR inhibitors, also known as rapamycin analogs (18). Sirolimus, originally developed as an anti-fungal agent (19), has antitumor activity that is exerted via binding to an intracellular protein (FKBP12), resulting in mTOR pathway inhibition and cell cycle arrest in the G1 phase (19,20). It has shown promising antitumor activity alone and in combination with other antitumor agents in preclinical (11,21) and clinical trials (22,23).

Based on the results of our phase I study that sirolimus has modest efficacy in advanced cancer with *PIK3CA* mutations/amplifications (24), we conducted a phase II study of the antitumor efficacy and safety of sirolimus in chemotherapy-refractory solid tumors with *PIK3CA* mutations.

Methods

Study design and treatment

A multi-center, open-label, single-arm prospective pilot study was conducted to evaluate the antitumor efficacy and safety of sirolimus in patients with solid tumors harboring *PIK3CA* mutations or amplifications. The study was conducted at 7 university hospitals in South Korea. Institutional Review Boards approved the protocol at all sites. All patients provided written informed consent. All study procedures followed the guidelines of the Declaration of Helsinki.

Oral sirolimus (1 mg daily) was administered

continuously in 28-day cycles until disease progression, occurrence of unacceptable toxicity, patient's request, or death due to any cause. The response was evaluated every 2 cycles from the start of the treatment based on the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). The primary endpoints were overall response rate (ORR) and safety. The secondary endpoints were disease control rate (DCR) and progression-free survival (PFS). All cases of toxicity were reviewed according to the National Cancer Institute Common Terminology Criteria of Adverse Events (CTCAE), version 4.03.

Patient eligibility

Eligible patients, 19 years of age or older, with pathologically confirmed solid tumors, who had undergone standard chemotherapy and had a confirmed *PIK3CA* mutation or amplification, as assessed by gene sequencing (CancerSCANTM or AxenTM) (24), were included. Further, patients were required to have at least one measurable or non-measurable lesion as per the revised response evaluation criteria in solid tumors (RECIST) v.1.1. (this lesion was evaluated at least 28 days before administration), Eastern Cooperative Oncology Group performance status 2 or lower, adequate hepatic [total bilirubin less than or equal to one and a half times the upper limit of normal (ULN)], aminotransferase (less than or equal to two and a half times the ULN), renal (adequate renal serum creatinine less than or equal to one and a half times the ULN), and hematologic (absolute neutrophil count of $\geq 1,500$ cells/mL, platelet count of $\geq 75,000$ cells/mL, and hemoglobin of ≥ 9 grams/dL) functions. Patients were also required to have appropriate heart function, without any clinically significant dysfunction that would require normal or medical intervention, as assessed by a 12-lead ECG and other history. All men and women of childbearing age had to use appropriate contraception.

Exclusion criteria were as follows: patients diagnosed with a malignant tumor other than a non-resistant solid tumor or a properly treated baseline or squamous cell skin cancer, history of hydrostatic or brain transfer (if the condition was previously treated properly and the patient was not currently receiving steroids as an anticonvulsant or for brain pressure control), and clinically significant gastrointestinal disorders that may cause a disturbance in the ingestion, distribution, or absorption of test drugs, such as that in the absence of the oral administration of purified water. Cardiovascular conditions within the last 6 months

(cardiovascular surgery, myocardial infarction, unstable angina, coronary artery bypass surgery, and peripheral cardiovascular disease), uncoordinated convulsions, and central nervous system disease or combined psychiatric illness, which would make it difficult for the subject to voluntarily agree to a clinical trial. Women with children were required to stop breastfeeding before the first dose of the test medication until 14 days after the last dose. Patients with active infections or other uncontrolled disease and those previously administered sirolimus were also excluded.

Statistical analysis

ORR was defined as the proportion of patients with a complete (CR) or partial response (PR) to sirolimus. DCR was defined as the proportion of patients with CR, PR, or stable disease (SD) in response to the treatment. PFS was calculated using the Kaplan-Meier method from the time of sirolimus treatment to disease progression, patient's request, or death due to any cause. Two-tailed P-values of <0.05 were considered significant. All analyses were performed using SPSS ver. 25.0 (IBM Corporation, Armonk, NY, USA).

Results

Patient characteristics

From July 2017 to March 2019, 24 patients with solid tumors harboring a *PIK3CA* mutation or amplification were treated with sirolimus. Most patients were female (66.6%) and had stage IV cancer (79.1%) at initial diagnosis. The median age at the initiation of sirolimus treatment was 57 years (range, 36–73 years). The most common type of cancer was colorectal cancer (29.1%), followed by sarcoma (16.6%), ovarian (12.5%), breast (8.3%), and lung cancer (8.3%), and others (cholangiocarcinoma, gallbladder, adrenal cortical, and stomach cancer, and unknown origin, 4.1% each).

H1047R and E545K were the most frequent *PIK3CA* mutations (16.6%), followed by amplification (12.5), E453K (8.3%), and E542K (8.3%). All patients had at least one second line of chemotherapy before sirolimus (median 4, range, 2 to 12). Patient characteristics are

summarized in *Table 1*.

Efficacy

Of 24 enrolled patients, 4 patients were excluded from the final analysis. Two patients had rapid disease progression-related death prior to the response evaluation, one patient withdrew consent and refused further treatment after 2 weeks, and one had a non-target lesion only. For the remaining 20 patients, baseline tumor measurements and response evaluations were performed.

Evaluable patients received a median of 2.26 cycles of sirolimus during a median follow up time of 6.1 months. The ORR was 0% (none of the patients showed CR or PR), and DCR was 30% (6 SD) after sirolimus treatment. Median PFS was 2.39 months [95% confidence interval (CI), 1.97–2.81 months], and PFS at 8 weeks was 75% (*Figure 1*).

Among the patients who were eligible for the response evaluation, the mean volume change was 15.83%. SD was documented in 6 patients and PD in 14 patients. Tumor volume decreases (–12.08% to –13.88%) were observed in 4 patients with SD (20%). One patient was classified as PD owing to a new lesion, despite a decrease in the target lesion. The best response and absolute values for tumor control are summarized in *Figure 2A*.

The median duration of response for patients with SD was 3.9 months (range, 2.53–8.83 months). The median duration for patients with PD was 2.2 months (range, 0.6–2.6 months). A swimmer plot of the sirolimus treatment duration for 20 evaluable patients is presented in *Figure 2B*. As per multivariate analysis, there were no independent prognostic factors for PFS.

Safety

During the treatment duration [median, 1.98 months (0.57–9.07 months)], 36 treatment-related adverse events were observed in the total population (n=24). Abdominal pain was the most common adverse event (20.8%), followed by fatigue (16.7%) and anemia (16.7%). In terms of severe adverse events (grade 3 or higher), anemia was the most common (16.7%), followed by fatigue, abdominal pain, and anorexia (8.3% each). No adverse events resulted in the

Table 1 Baseline characteristics of the total population

Patient number	Sex	Age	Histology	Stage at diagnosis	PIK3CA mutation	Sirolimus CTx (line)	Best Response	PFS (weeks)	Comments
1	F	54	Breast	I	H1047R	10	PD	1.87	
2	F	72	Sarcoma	IV	R818H	5	SD	2.53	
3	F	58	Colorectal	IV	H1047R	6	PD	1.27	
4	F	45	Gallbladder	IV	Q546K	3	PD	1.83	
5	M	73	Cholangiocarcinoma	IV	E453K	3	NA	1.80	Expired prior to disease evaluation
6	F	57	MUO	Unknown	E545K	9	PD	2.67	
7	M	37	Lung	IV	G545L	4	PD	0.60	
8	F	42	GBM	Unknown	R38S	4	SD	5.03	Ongoing
9	F	57	Ovarian	IV	E493X	10	NA	0.97	Non-target lesion
10	M	57	Stomach	IV	E453K	5	PD	2.00	
11	F	56	Colorectal	IV	E542K	5	PD	2.23	
12	F	48	Colorectal	IV	H1047R	4	PD	1.97	
13	M	61	Lung	IV	Amp	4	NA	1.10	Expired prior to disease evaluation
14	F	68	Sarcoma	IV	E545K	3	SD	3.87	
15	F	59	Colorectal	IV	E365K	4	PD	1.73	
16	F	57	Breast	III	Amp	3	SD	3.93	
17	M	65	Sarcoma	IV	Amp	5	PD	1.90	
18	F	45	Colorectal	IV	E545K	4	PD	2.27	
19	F	36	Ovarian	IV	E542K	6	NA	0.70	Withdrawal
20	M	40	Colorectal	III	E545K	7	PD	2.40	
21	M	53	Adrenal cortical	IV	G545A	3	PD	2.53	
22	M	62	Colorectal	IV	G106V	5	PD	2.23	
23	F	50	Sarcoma	IV	PTEN loss	13	SD	8.83	Ongoing
24	F	55	Ovarian	IV	H1047R	8	SD	2.80	

CTx, chemotherapy; MUO, malignancy of unknown origin; GBM, glioblastoma multiforme; amp, amplification.

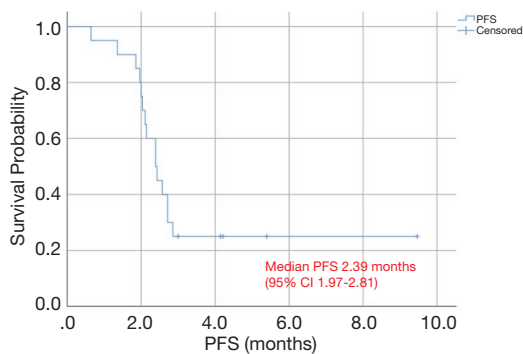


Figure 1 Kaplan-Meier curves. PFS for eligible patients with solid tumors harboring a PIK3CA mutation or amplification treated with sirolimus. PFS, progression-free survival; CI, confidence interval.

discontinuation of treatment. The safety profile for the total population is provided in *Table 2*.

Discussion

We comprehensively evaluated the clinical antitumor efficacy and safety of sirolimus monotherapy for patients with refractory solid tumors harboring PIK3CA aberrations. The efficacy of mTOR inhibitors for the treatment of advanced cancers is controversial (25-31). mTOR inhibitor monotherapy in pancreatic neuroendocrine tumors showed a survival benefit compared with a placebo group (11.0 vs. 4.6 months, P<0.001) (26). Temsirolimus single-agent therapy for advanced non-small cell lung cancer showed

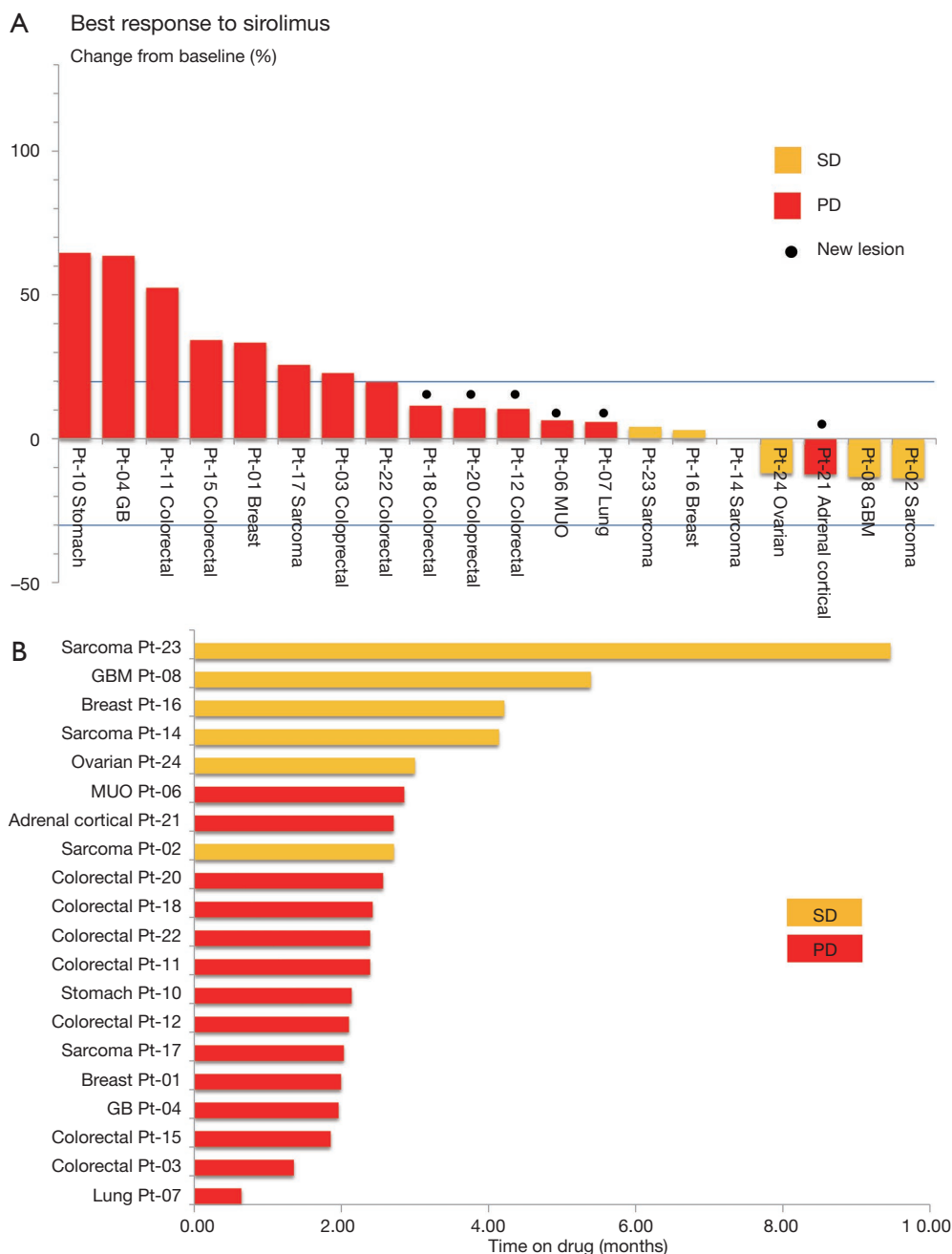


Figure 2 Response data for eligible patients with solid tumors harboring a PIK3CA mutation or amplification treated with sirolimus. (A) Waterfall plot of eligible patients with solid tumors harboring a PIK3CA mutation or amplification treated with sirolimus. Four patients (20%) had some tumor shrinkage, including three with SD and one with PD (new lesion). The y-axis indicates the percentage of maximum tumor reduction assessed according to RECIST 1.1 criteria. (B) Swimmer plot of treatment duration for 20 evaluable patients with solid tumors harboring a PIK3CA mutation or amplification. SD, stable disease; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; CCC, cholangiocarcinoma; GB, gallbladder; MUO, malignancy of unknown origin; GMB, glioblastoma multiforme.

Table 2 Treatment-related adverse events

Adverse events	Any grade		Grade ≥ 3	
	N	%	N	%
Anemia	4	16.7	4	16.7
Thrombocytopenia	1	4.2	1	4.2
Neutropenia	1	4.2	1	4.2
Fatigue	4	16.7	2	8.3
Abdominal pain	5	20.8	2	8.3
Anorexia	3	12.5	2	8.3
Nausea	2	8.3	0	0
Constipation	1	4.2	0	0
Ascites	1	4.2	1	4.2
Rash	1	4.2	0	0
Dry skin	1	4.2	0	0
Confusion	1	4.2	1	4.2
Fever	2	8.3	0	0
Sore throat	2	8.3	0	0
Dyspnea	1	4.2	0	0
Pleural effusion	1	4.2	1	4.2
Urinary tract infection	2	8.3	0	0
Upper respiratory infection	2	8.3	0	0
Duodenal hemorrhage	1	4.2	1	4.2

modest clinical activity (median PFS, 2.3–2.7 months) (30,31). However, mTOR inhibitor monotherapy in patients with gastric cancer was ineffective, with an ORR of 0% and PFS of 2.7 months in a phase II trial (27) and a PFS of 1.7 months in a phase III trial (28). Similar results were obtained for breast cancer (with a reported median TTP of 3 months) (29). However, patient selection in these studies did not consider biomarkers, such as PIK3CA-AKT-mTOR mutations.

Studies of genetic alterations in the PIK3CA-AKT-mTOR pathway have also yielded controversial results. Everolimus monotherapy in pS6 (Ser240/4)-mutated gastric cancer was associated with a prolonged PFS (2.76 *vs.* 1.57 months, $P < 0.001$) (32). In the MOSCATO 01 trial, therapies targeting genetic alterations, including PIK3CA mutations, improved clinical outcomes (33). However, in a trial of molecularly targeted therapy based

on tumor molecular profiling versus conventional therapy for advanced cancer (SHIVA), everolimus failed to show a significant benefit with regard to PFS compared to conventional therapy (median PFS 2.4 *vs.* 1.9 months, $P = 0.30$) (34).

Notably, one patient with metastatic sarcoma with no response to at least eight regimens, including doxorubicin and ifosfamide, gemcitabine, pazopanib, and nivolumab, demonstrated long-term SD for >12 months. Consistent with these results, the phase III SUCCEED trial demonstrated a significantly lower risk of progression (by 28%) in the deforolimus (ridaforolimus, MK-8669) maintenance arm than in the placebo group (hazard ratio = 0.72, $P < 0.0001$) (35). Patients with sarcoma often harbor mutations in the mTOR signaling pathway, which are related to the antitumor activity of deforolimus in phase I and phase

II trials when administered as maintenance therapy. Sirolimus is widely used as an immunosuppressive agent following transplantation. In post-transplant patients, sirolimus causes the regression of Kaposi's sarcoma and renal angiomyolipomas in tuberous sclerosis (36,37). As the patent for the anti-cancer application of sirolimus expired in 1993, other rapalogs, such as temsirolimus, everolimus, and deforolimus have been developed (36).

Most recently, nab-sirolimus (ABI-009) has been developed as an albumin-bound mTOR inhibitor to increase tumor intake. A phase II trial of ABI-009 for advanced malignant perivascular epithelioid cell tumors (PEComa) demonstrated an ORR of 42% (38). Hence, the role of rapalogs as anti-cancer treatment for refractory cancer is a focus of current research.

Despite the insufficient efficacy of monotherapies, there is evidence that the use of mTOR inhibitors in combination with other drugs could provide a clinical benefit. The combination of sirolimus and pemetrexed exhibited meaningful antitumor activity in pretreated advanced non-small cell lung cancer (23). The combination of trastuzumab plus vinorelbine significantly prolonged PFS in trastuzumab-resistant HER2-positive breast cancer (39). Collectively, mTOR inhibitors are more effective for tumor stabilization than reduction. The use mTOR inhibitors in combination with other antitumor agents might have synergistic effects.

However, our study had several limitations. The relatively small number of patients and heterogeneity of cancer types could preclude a precise analysis of the association between PIK3CA mutations and the efficacy of sirolimus therapy. The heavily pre-treated nature of the patients could indicate a high mutation burden in tumors, suggesting the co-existence of other tumorigenic genetic alterations. Finally, sirolimus only inhibits mTORC1 activity and not the mTORC2-mediated cascade; accordingly, it only partially inhibits the mTOR pathway. Considering the complicated signaling cascade and various cross signaling reactions with other pathways, sirolimus alone was not sufficient to evaluate the true association between PIK3CA mutation or amplification and mTOR inhibitor efficacy.

Recently developed next-generation mTOR inhibitors blocking multiple targets in the PIK3CA-AKT-mTOR pathway show promising efficacy in various tumors (40-42). Further studies are needed to establish the roles of mTOR inhibitors in individualized cancer treatment and validate the prognostic value of biomarkers.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2020.04.07>). SB reports grants from Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), grants from Ministry of Health & Welfare, Republic of Korea, non-financial support from Korean Cancer Study Group and KCSG data center, during the conduct of the study. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Institutional Review Boards approved the protocol at all sites (No. SMC 2016-02-052-040). All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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