

# Everolimus Versus Sirolimus for Angiomyolipoma Associated with Tuberous Sclerosis Complex: A Multi-Institutional Retrospective Study in China

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## Research Article

**Keywords:** Tuberous Sclerosis Complex, Everolimus, Sirolimus, Treatment Outcome, Adverse events

**Posted Date:** March 17th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-305370/v1>

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# Abstract

## Purpose

To evaluate the efficacy and safety of everolimus and sirolimus in patients with tuberous sclerosis complex-associated angiomyolipomas (TSC-AML).

## Materials and Methods

We performed a multi-institutional retrospective study of TSC-AML patients treated with oral everolimus or sirolimus.

Angiomyolipoma volume was estimated using orthogonal measurements by MRI or CT. Adverse events (AEs) were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events. All analyses were performed using SPSS 19.0 software.

## Results

There were high response rates in both two groups. With the prolonged medication time, the therapeutic efficacy of two agents became more significant. Everolimus had a more significant TSC-AML volume reduction after 6 and 12 months than sirolimus. More than 1/2 of everolimus patients had  $\geq 50\%$  reduction and approximately 80% of them had  $\geq 30\%$  reduction, higher than that of the sirolimus patients. Regarding safety, there was no significant difference in the incidence of AEs between the two groups.

And the most common AE was oral mucositis.

## Conclusions

Both everolimus and sirolimus are excellent therapeutic choices for TSC-AML. However, everolimus had a better therapeutic efficacy than sirolimus, especially in reducing TSC-AML volume. Therefore, everolimus is recommended as the first choice.

## Introduction

Tuberous sclerosis complex (TSC) is a hereditary disorder with an incidence of 1:6,000–1:10,000. It is characterized by prominent neurodevelopmental features and hamartomas in multiple organs in the body, including brain, heart, lungs, bones, and especially kidneys(1). Among the renal phenotypes of TSC, renal angiomyolipoma (AML) is the most common type affecting up to 80% of patients with TSC, which can lead to chronic kidney disease (CKD) and intrarenal hemorrhage(2). Considering that renal disease is a leading cause of death or disability, second only to neurologic disease across the populations(3),

clinicians have paid more attention to the renal involvement in TSC and actively seek more optimal treatment strategies.

TSC is an autosomal dominant disorder caused by mutations in either TSC1 or TSC2 gene. TSC1 and TSC2, together with a third subunit, TBC1D7, form a functional complex and act as important repressors upstream of the mammalian target of rapamycin (mTOR). TSC1/TSC2 mutations will cause the dysfunction of the complex, resulting in the activation of mTOR signaling pathway. This may serve a critical role underlying the pathogenesis of benign tumors or hamartomas in multiple systems(4). Based on this pathogenic mechanism, mTOR inhibitors have been considered as a novel therapy for TSC. Previous cohort studies have corroborated the therapeutic effect of mTOR inhibitors against TSC related complications, including subependymal giant cell astrocytomas, renal AML, seizure, facial angiofibromas, etc(5–8).

First isolated from *Streptomyces hygroscopicus* in a soil sample from Easter Island in 1975, sirolimus, a kind of mTOR inhibitor, has demonstrated prodigious efficacy in past decades(9). Everolimus (RAD001) is derived from sirolimus has many advantages, such as better pharmacokinetics, better absorption, higher oral bioavailability, faster steady-state blood concentration after administration, and faster elimination after withdrawal(10–12), besides, certain study showed that everolimus could preserve renal function in most patients(13). However, the high economic costs and strict indications limit the accessibility and utilization of everolimus in Chinese mainland, as the price of everolimus is currently about ¥ 8800 per month, even up to ¥ 15000 per month before being included in medical insurance. While the price of sirolimus is only ¥ 3200 per month, or even ¥ 1000 per month for domestic ones, and the indication for the use of it is not such strict.

Clinical studies have suggested that TSC-AML (diameter  $\geq$  3cm) could respond to sirolimus or everolimus therapy(14, 15). And we also have confirmed that TSC-AML regressed somewhat during everolimus therapy in a Chinese cohort(16). However, there are no studies comparing outcomes of TSC patients undergoing everolimus or sirolimus treatment. Here, we report a multi-institutional retrospective study in China comparing the efficacy and safety of everolimus and sirolimus in TSC-AML patients.

## Methods

### Study design and patient population

This was a multi-institutional retrospective cohort study, and it was carried out in accordance with the Declaration of Helsinki(17).

Research data were derived from approved Xiangya Hospital of Central South University, Peking Union Medical College Hospital and The Affiliated Hospital of Qingdao University.

All patients signed written informed consent to voluntarily participate in this cohort.

Inclusion criteria was that 1)  $\geq$  18 years of age; 2) presented between September 2014 and September 2020 to the department of urology; 3) with a definite diagnosis of TSC; 4) with at least one AML whose

diameter  $\geq$  30 mm; 5) treated with oral everolimus or sirolimus monotherapy.

We enrolled patients who received oral everolimus 10 mg or sirolimus 2 mg per day for more than 3 months and got at least once radiographic follow-up and safety evaluation. The primary efficacy endpoint was the proportion of patients with confirmed AML response of at least a 50% reduction in total volume of target AML relative to baseline.

## Treatment and adverse events evaluation

At baseline, angiomyolipomas were visualized and measured by abdominal computed Tomography (CT) or magnetic resonance imaging (MRI), and the modality was kept consistent throughout the study for each patient. Up to four angiomyolipomas with maximum diameters  $\geq$  3.0 cm were identified as target lesions, and the sum of these diameters was obtained for each patient.

During the follow-up period, physical examination, routine blood analysis, routine urine analysis and radiographic evaluation of the kidneys were performed at 3, 6, 12, 18, 24 months. Tumor response was assessed with Response Evaluation Criteria in Solid Tumors (RECIST version 1.1), while adverse events (AEs) were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0).

## Statistical analysis

Continuous variables were reported as mean  $\pm$  standard deviation (M  $\pm$  SD) and categorical variables were reported as frequency counts and percentages (%). All statistical analyses were performed with SPSS software, version 19.0 (SPSS, Chicago, IL, USA). The Student's *t*-tests and the Mann-Whitney U test were used to compare continuous variables, as appropriate. All reported *p* values were 2-sided and *p* < 0.05 was considered statistically significant.

## Results

### Patient characteristics

In the cohort, a total of 124 TSC-AML patients from three clinical centers were reviewed. They were divided into sirolimus group (*n* = 33) and everolimus group (*n* = 91) according to the monotherapy they received. Baseline demographic characteristics were generally balanced between the two treatment groups (Tables 1). In general, patients in everolimus group had relatively more severe renal phenotypes than patients in sirolimus group, including more target AML lesions ( $\geq$  3cm) and larger size of target AML. Regarding to TSC-AML, 3 ~ 4 of target AML lesions ( $\geq$  3 cm) were observed in 19 (58%) patients in the sirolimus group, while in 57 (63%) patients in the everolimus group. The median maximum diameters of target AML at baseline were 6.1 (3.5–16) cm and 8.1 (3.1–22) cm in the sirolimus and everolimus groups, respectively. In addition, 36 (40%) patients in everolimus group had received prior surgery/invasive procedure, and similarly, 15 (45%) patients in sirolimus group had received such treatment.

Table 1  
Baseline demographic and clinical characteristics.

	<b>Sirolimus</b> <b>n = 33 (%)</b>	<b>Everolimus</b> <b>n = 91 (%)</b>
<b>Age in years, median(range)</b>	30 (19–59)	29 (18–52)
<30 year	16 (48)	51 (56)
≥30 year	17 (52)	40 (44)
<b>Sex</b>		
Male	10 (30)	34 (37)
Female	23 (70)	57 (63)
<b>LAM (female)</b>	5 (22)	11 (19)
<b>≥ 1 Skin lesion</b>	31 (94)	89 (98)
<b>SEGA</b>	2 (6)	5 (5)
<b>Maximum diameter of target AML</b>		
Median (range, cm)	6.1 (3.5–16)	8.1 (3.1–22)
≥ 8 cm	12 (36)	48 (53)
≥ 4 cm and < 8 cm	16 (48)	37 (41)
≥ 3 cm and < 4 cm	5 (15)	6 (6)
<b>Number of target AML lesions (≥ 3cm)</b>		
1 ~ 2	14 (42)	34 (37)
3 ~ 4	19 (58)	57 (63)
<b>Surgery/invasive procedure</b>	15 (45)	36 (40)
Renal embolisation	5 (15)	21 (23)
Partial nephrectomy	7 (21)	10 (11)
Nephrectomy	6 (18)	11 (12)
NOTE: Descriptive statistics are frequencies and percentages or otherwise specified. AML: angiomyolipoma; LAM: lymphangioliomyomatosis; SEGA: subependymal giant cell astrocytoma.		

## Treatment efficacy and monthly costs

First, we compared the changes in target AML volume between these two groups. With the extension of time, the number of patients who insist on medication in the two groups gradually decreased, and the percentage of patients with tumor reduction ( $\geq 30\%$  &  $\geq 50\%$ ) gradually increased. At all four follow-up

points, the percentage of patients with tumor reduction ( $\geq 30\%$  &  $\geq 50\%$ ) in everolimus group was higher than that in sirolimus group (Fig. 2. A). In general, everolimus surpassed sirolimus as it achieved better outcomes and demonstrated higher efficacy, as more patients in everolimus group achieved more than 60% tumor volume reduction, even up to 85% tumor reduction. It's worth noting that more than half of patients in everolimus group achieved  $\geq 50\%$  reduction of target AML lesions from baseline. In contrast, less than half of the sirolimus patients achieved  $\geq 50\%$  reduction, and most of them fall within the range of 50%–60% reduction. Moreover, regarding the patients with  $\geq 30\%$  tumor reduction after treatment, the percentage in everolimus group was also higher than that in sirolimus group (Fig. 1. B-C).

Patient 1 and 2 were identified as representative cases in the everolimus and sirolimus groups, since they presented with a remarkable reduction of target AML volume, which could be visualized on MRI (Fig. 2).

Moreover, we set the decrease from baseline and response rate as variables to compare efficacy of the two drugs (Table 2). Almost all patients showed a great response to mTOR inhibitors treatment. And with the extension of medication time, the decrease from baseline became more and more obvious, the response rate gradually increased as well. After 3 months of treatment, sirolimus and everolimus groups showed similar response rate (33% vs. 46%) and similar decrease from baseline ( $35.4 \pm 16.2\%$  vs.  $42.0 \pm 17.6$ ). Intriguingly, after prolonged treatment, everolimus showed higher efficacy than sirolimus on decrease from baseline (6 months:  $48.5 \pm 20.6\%$  vs.  $38.1 \pm 17.2\%$ ,  $P = 0.01$ ; 12 months:  $56.7 \pm 21.2\%$  vs.  $45.1 \pm 13.9\%$ ,  $P = 0.02$ ). However, no statistical difference was found in the response rates between the two groups at these two follow-up points (6 months: 38% vs. 55%; 12 months: 52% vs. 69%). At last follow-up point of 24 months, the response rate (60% vs. 81%) and decrease from baseline ( $52.5 \pm 14.1\%$  vs.  $62.5 \pm 15.3\%$ ) didn't exhibit any significant differences between sirolimus and everolimus groups.

Table 2  
Treatment efficacy.

	<b>Sirolimus n = 33 (%)</b>	<b>Everolimus (%) n = 91(%)</b>	<b>P-Value</b>
<b>3 months</b>			
Decrease from baseline (mean ± SD, %)	35.4 ± 16.2	42.0 ± 17.6	0.06
No. PR (%)	11 (33)	42 (46)	0.20
<b>6 months</b>			
Decrease from baseline (mean ± SD, %)	38.1 ± 17.2	48.5 ± 20.6	0.01
No. PR (%)	12 (38)	46 (55)	0.09
<b>12 months</b>			
Decrease from baseline (mean ± SD, %)	45.1 ± 13.9	56.7 ± 21.2	0.02
No. PR (%)	12 (52)	34 (69)	0.22
<b>24 months</b>			
Decrease from baseline (mean ± SD, %)	52.5 ± 14.1	62.5 ± 15.3	0.09
No. PR (%)	6 (60)	17 (81)	0.77
NOTE: Target angiomyolipomas in the kidney in each patient were visualized by CT or MRI at baseline and at 3, 6, 12, 18 and 24 months and the longest diameter of each angiomyolipoma was measured. PR: partial response, defined as a reduction in angiomyolipoma volume (sum of volumes of all target angiomyolipomas identified at baseline) of 50% or more relative to baseline and absence of angiomyolipoma progression.			

Table 3  
Everolimus/Sirolimus-related adverse events.

	Sirolimus n = 33 (%)		Everolimus n = 91 (%)		P-value All grades
	All grades	Grade 3-4	All grades	Grade 3-4	
<b>Gastrointestinal</b>					
Mucositis oral	30(91)	4(12)	89 (98)	11 (12)	0.11
Diarrhea	4(12)	0	5 (5)	0	0.21
Vomiting	0	0	3 (3)	0	0.29
Constipation	2(6)	0	1 (1)	0	0.11
<b>Gynaecological</b>					
Irregular menstruation (female)	7 (30)	3 (13)	25 (44)	9 (15)	0.07
<b>Metabolic</b>					
Hypertriglyceridemia	11(33)	0	30(33)	0	0.96
Cholesterol high	4(12)	0	11(12)	0	0.99
Proteinuria	2(6)	0	8(9)	0	0.62
ALP increased	4(12)	0	8(9)	0	0.58
GGT increased	2(6)	0	5(5)	0	0.90
Hypophosphatemia	0	0	3(3)	0	0.29
<b>Infection</b>					
Upper respiratory infection	11(33)	0	22(24)	0	0.31
Pneumonitis	4(12)	2(6)	5(6)	3(3)	0.21
Urinary tract infection	4(12)	0	5(6)	0	0.21
<b>Dermatology</b>					
Rash acneiform	6(18)	0	16(18)	3(3)	0.94
<b>Constitutional symptoms</b>					
Abdominal pain	4(12)	0	11(12)	0	0.99
Headache	4(12)	0	3(3)	0	0.06
Malaise	2(6)	0	3(3)	0	0.49

NOTE: Everolimus/Sirolimus-related adverse reactions were those adverse events that were considered to be possibly, probably, or definitely related to everolimus/sirolimus.

	Sirolimus n = 33 (%)		Everolimus n = 91 (%)		P-value
	All grades	Grade 3–4	All grades	Grade 3–4	All grades
<b>Soft tissues</b>					
Peripheral oedema	4(12)	2(6)	3(3)	0	0.06
<b>Blood</b>					
Neutrophil count decreased	2(6)	0	3(3)	0	0.49
Lymphocyte count decreased	0	0	3(3)	0	0.29
Anemia	2(6)	0	1 (1)	0	0.11
NOTE: Everolimus/Sirolimus-related adverse reactions were those adverse events that were considered to be possibly, probably, or definitely related to everolimus/sirolimus.					

## Adverse events

No unexpected AEs were reported. A variety of common AEs have also been reported in both sirolimus and everolimus groups without statistical differences, including oral mucositis (91% vs 98%), irregular menstruation (30% vs 44%), hypertriglyceridemia (33% vs 33%), upper respiratory infection (33% vs 24%), rash acneiform (18% vs 18%), etc. Grade 3 or 4 AEs occurred in 11 (33%) and 26 (29%) patients in the sirolimus and everolimus groups, respectively. No unexpected AEs were reported. No patient refused treatment or exited the cohort due to AEs, and no mortality was reported during medication.

## Discussion

The relatively low economic expenditure of sirolimus has prompted the choice of sirolimus over everolimus for many TSC-AML patients under low economic conditions. However, whether sirolimus can achieve considerable curative effect and become an alternative choice of everolimus for TSC-AML patients with low economic status. To the best of our knowledge, this Chinese multi-institutional retrospective study is the first to compare the efficacy of everolimus and sirolimus for the treatment of TSC-AML patients.

We enrolled a total of 124 TSC patients with at least one TSC-AML (diameter  $\geq$  30 mm) who received sirolimus or everolimus monotherapy to compare their efficacy. In the cohort, 33 patients were treated with sirolimus and remaining 91 patients were treated with everolimus. At baseline, the renal phenotype associated with TSC in everolimus group was relatively more severe compared to sirolimus group, as reflected by the quantities and sizes of target AML lesions.

The changes in target AML volume exploratory study showed a considerable improvement in the volume of target AML with the mTOR inhibitors treatment, consistent with previous studies(14, 15). In the everolimus group, more than half of patients had  $\geq$  50% reduction from baseline of target AML lesions, and approximately 80% patients had  $\geq$  30% reduction. This is basically in agreement with the

efficacy of everolimus reported previously (6). In terms of the percentage of patients with tumor reduction ( $\geq 30\%$  &  $\geq 50\%$ ), everolimus surpassed sirolimus as it achieved better outcomes and demonstrated higher efficacy. Further statistical analysis also demonstrated both agents could achieve high response rate and significant tumor reduction. And with the extension of medication time, the efficacy was more and more obvious. This confirms that everolimus and sirolimus, as mTOR inhibitors, do have definite efficacy in the treatment of TSC-AML as both of them can significantly reduce TSC-AML volume. Importantly, everolimus outperformed to sirolimus in decreasing the target AML volume after 6 months and 12 months of medication although there was no statistical difference in the response rate between the two groups. In general, it was showed that everolimus has more obvious advantages than sirolimus in the TSC-AML treatment in our study. Of interest, after 24 months, everolimus didn't lead to more significant reduction in tumor volume than sirolimus as expected, which may be attributed to the limited number of patients who received medication for 24 months. Generally speaking, patients are more likely to seek alternative treatment if the drug therapy fails. Thus, only 31 patients persisted with medication for 24 months, including 21 in everolimus group and 10 in sirolimus group. The lower sample size at follow-up after 24 months reduces the reliability of the long-term efficacy comparison between everolimus and sirolimus. Studies with larger sample size and sustained follow-up are needed to compare the long-term efficacy of the two agents. In addition, A previous study found a trend toward larger volume in TSC-AML after cessation of mTOR inhibitors therapy, which was also reported in our previous work(14, 16). Thus, it is important to assess whether continuous mTOR inhibitors is necessary to maintain the reduction in the total volume of target AML.

The safety evaluations showed that everolimus and sirolimus had a similar and acceptable safety profile with no statistical difference in our cohort. The types and incidence of AEs were consistent with other cohort studies, including oral mucositis, irregular menstruation, hypertriglyceridemia, upper respiratory infection, rash acneiform, etc(5, 15).

Among those AEs, oral mucositis stood as the most common type (91% in sirolimus group; 98% in everolimus group).

AEs of grade 3 or 4 only occurred in a small part of patients, which further confirms the safety of mTOR inhibitors used in TSC-AML treatment. Of course, there were serious AEs reported while patients were receiving sirolimus. Bissler JJ attributed it to patients' basic condition, as these patients themselves suffered from chronic, slowly progressive diseases(14). This may also explain why part of our patients suffered from AEs of grade 3 or 4. It also reminds us that we should be especially cautious in employing sirolimus to these patients with chronic diseases. Similar to previous studies, oral mucositis with high incidence was observed in our study, suggesting the need for appropriate monitoring and management(5, 15). Theoretically, mTOR inhibitors can promote the release of keratinocyte cytokines, directly cause epithelial injury, and eventually lead to stomatitis(18). Of course, the details may be more complicated and require further exploration and verification at the molecular and animal levels. In order to avoid oral mucositis, patients should be instructed to maintain good oral hygiene by the frequent mouth wash using non-alcoholic reagents like 0.9% normal saline(19). To alleviate oral mucositis, topical treatment with sucralfate or oral rinses with dexamethasone are recommended(19, 20). In addition to oral mucositis,

irregular menstruation also occurs frequently in female patients, accounting for about 30% in sirolimus group and 44% in everolimus group, which has been frequently reported before(6, 8, 15). Disturbed hormone levels and ovarian cysts associated with mTOR inhibitor therapy have also been described(21–23), although the concrete mechanism was unknown. As reported in a two-year trial in China, more than 90% of women experienced amenorrhea subsequent to the mTOR inhibitors therapy(16), which was much higher than our results. Therefore, cohorts with large sample size are required to determine whether irregular menstruation is potentially a mTOR inhibitors-associated AE of restricting their use. And the specific mechanisms should be further investigated. Certainly, our results also remind clinician that monitoring for this potential side-effect is warranted in female patients of child-bearing potential.

There were several limitations in our study. Firstly, the sample size enrolled in our cohort is not big enough, especially at the follow-up point of 24 months after medication. Future studies focusing on this filed should employ more independent cohorts with larger sample sizes to investigate the underlying relationships. Secondly, we did not measure the blood concentration of everolimus or sirolimus, which can not only make the results more convincing and but also improve safety monitoring. Finally, a small number of patients in the sirolimus group chose domestic sirolimus due to economic considerations. We assumed that the efficacy of domestic sirolimus is equivalent to that of imported sirolimus, but whether their efficacies are consistent remains unknown, which needs further verification.

## **Conclusions**

In view of the efficacy and safety associated with reductions in target AML in TSC patients, both everolimus and sirolimus are good therapeutic choices. Although sirolimus requires less economic expenditure, everolimus demonstrates higher therapeutic efficacy especially in reducing TSC-AML volume. Therefore, we recommend everolimus as the first-line treatment, especially for patients with more severe TSC- AML.

## **Declarations**

### **Ethics Approval and Consent to Participate**

The study was done in accordance with the Declaration of Helsinki and local regulations. This study was approved by the Institutional Review Board of all participating sites. All patients signed written informed consent to participate.

### **Consent for publication**

The patients with individual person's data presented have signed written informed consent to publish.

### **Availability of data and material**

Please contact author for data requests.

## Competing Interests

The authors have nothing to disclose.

## Funding

This research was supported by the National Natural Science Foundation of China (81800590, 81670611, 81874094, 81902858, 81974397) and Natural Science Foundation of Hunan Province (2020JJ5882, 2020JJ5949).

## Authors' contributions

CL and YC participated in its design and coordination and drafted the manuscript. CL and YSZ participated in the design of the study and performed the statistical analysis. YSZ, MXZ, MFC, HZL, XBZ, LQ and YL conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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## Tables

**Table 1. Baseline demographic and clinical characteristics.**

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≥ 3 cm and < 4 cm	5 (15)	6 (6)
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1~2	14 (42)	34 (37)
3~4	19 (58)	57 (63)
<b>Surgery/invasive procedure</b>	15 (45)	36 (40)
Renal embolisation	5 (15)	21 (23)
Partial nephrectomy	7 (21)	10 (11)
Nephrectomy	6 (18)	11 (12)

NOTE: Descriptive statistics are frequencies and percentages or otherwise specified. AML: angiomyolipoma; LAM: lymphangiomyomatosis; SEGA: subependymal giant cell astrocytoma.

**Table 2. Treatment efficacy.**

	Sirolimus n=33 (%)	Everolimus (%) n=91(%)	P-Value
<b>3 months</b>			
Decrease from baseline (mean±SD, %)	35.4±16.2	42.0±17.6	0.06
No. PR (%)	11 (33)	42 (46)	0.20
<b>6 months</b>			
Decrease from baseline (mean±SD, %)	38.1±17.2	48.5±20.6	0.01
No. PR (%)	12 (38)	46 (55)	0.09
<b>12 months</b>			
Decrease from baseline (mean±SD, %)	45.1±13.9	56.7±21.2	0.02
No. PR (%)	12 (52)	34 (69)	0.22
<b>24 months</b>			
Decrease from baseline (mean±SD, %)	52.5±14.1	62.5±15.3	0.09
No. PR (%)	6 (60)	17 (81)	0.77

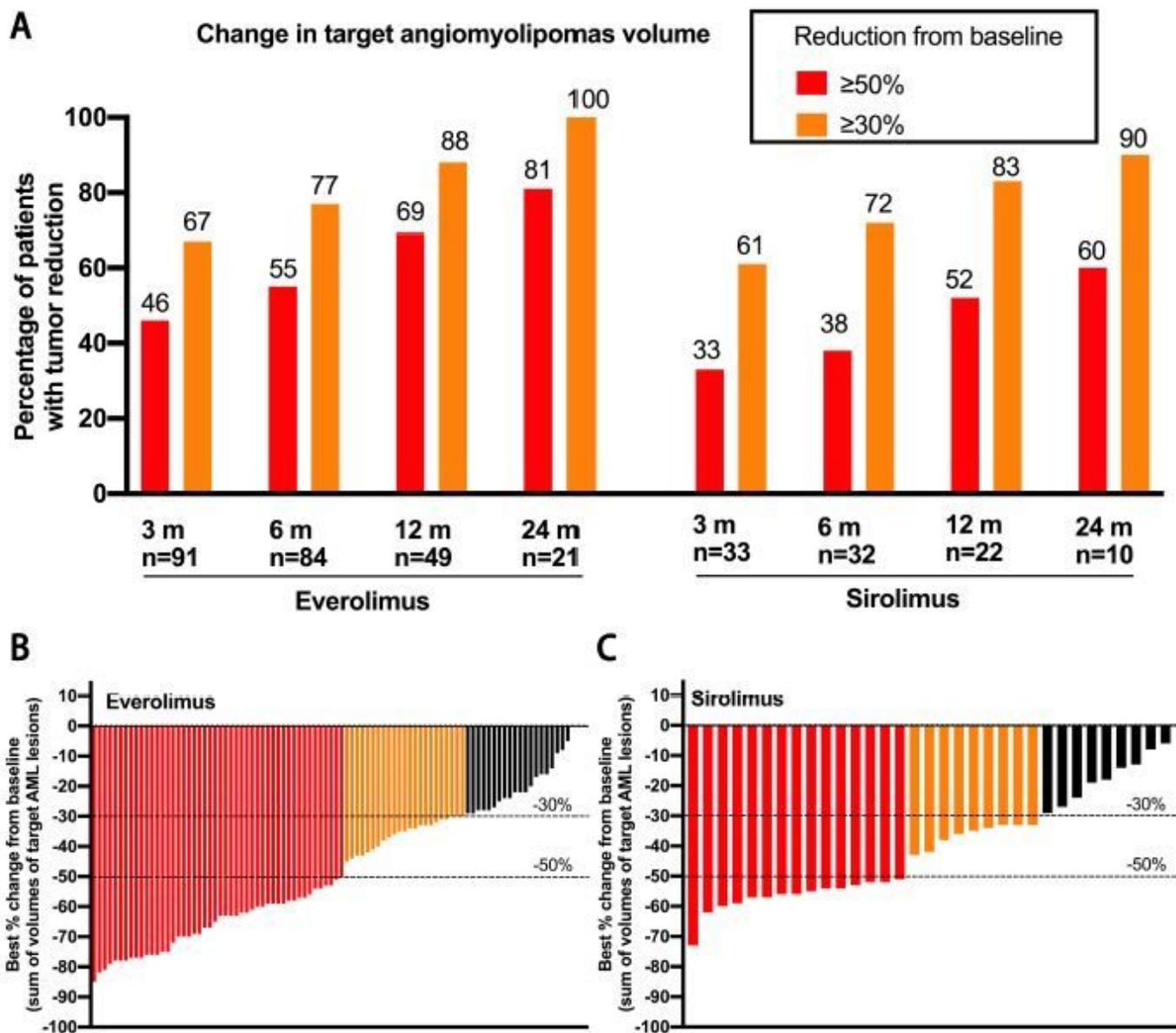
NOTE: Target angiomyolipomas in the kidney in each patient were visualized by CT or MRI at baseline and at 3, 6, 12, 18 and 24 months and the longest diameter of each angiomyolipoma was measured. PR: partial response, defined as a reduction in angiomyolipoma volume (sum of volumes of all target angiomyolipomas identified at baseline) of 50% or more relative to baseline and absence of angiomyolipoma progression.

**Table 3. Everolimus/Sirolimus-related adverse events.**

	Sirolimus n=33 (%)	Everolimus n=91 (%)	<i>P</i> -value		
	All grades	Grade 3-4	All grades	Grade 3-4	
<b>Gastrointestinal</b>					
Mucositis oral	30(91)	4(12)	89 (98)	11 (12)	0.11
Diarrhea	4(12)	0	5 (5)	0	0.21
Vomiting	0	0	3 (3)	0	0.29
Constipation	2(6)	0	1 (1)	0	0.11
<b>Gynaecological</b>					
Irregular menstruation (female)	7 (30)	3 (13)	25 (44)	9 (15)	0.07
<b>Metabolic</b>					
Hypertriglyceridemia	11(33)	0	30(33)	0	0.96
Cholesterol high	4(12)	0	11(12)	0	0.99
Proteinuria	2(6)	0	8(9)	0	0.62
ALP increased	4(12)	0	8(9)	0	0.58
GGT increased	2(6)	0	5(5)	0	0.90
Hypophosphatemia	0	0	3(3)	0	0.29
<b>Infection</b>					
Upper respiratory infection	11(33)	0	22(24)	0	0.31
Pneumonitis	4(12)	2(6)	5(6)	3(3)	0.21
Urinary tract infection	4(12)	0	5(6)	0	0.21
<b>Dermatology</b>					
Rash acneiform	6(18)	0	16(18)	3(3)	0.94
<b>Constitutional symptoms</b>					
Abdominal pain	4(12)	0	11(12)	0	0.99
Headache	4(12)	0	3(3)	0	0.06
Malaise	2(6)	0	3(3)	0	0.49
<b>Soft tissues</b>					
Peripheral oedema	4(12)	2(6)	3(3)	0	0.06
<b>Blood</b>					
Neutrophil count decreased	2(6)	0	3(3)	0	0.49
Lymphocyte count decreased	0	0	3(3)	0	0.29
Anemia	2(6)	0	1 (1)	0	0.11

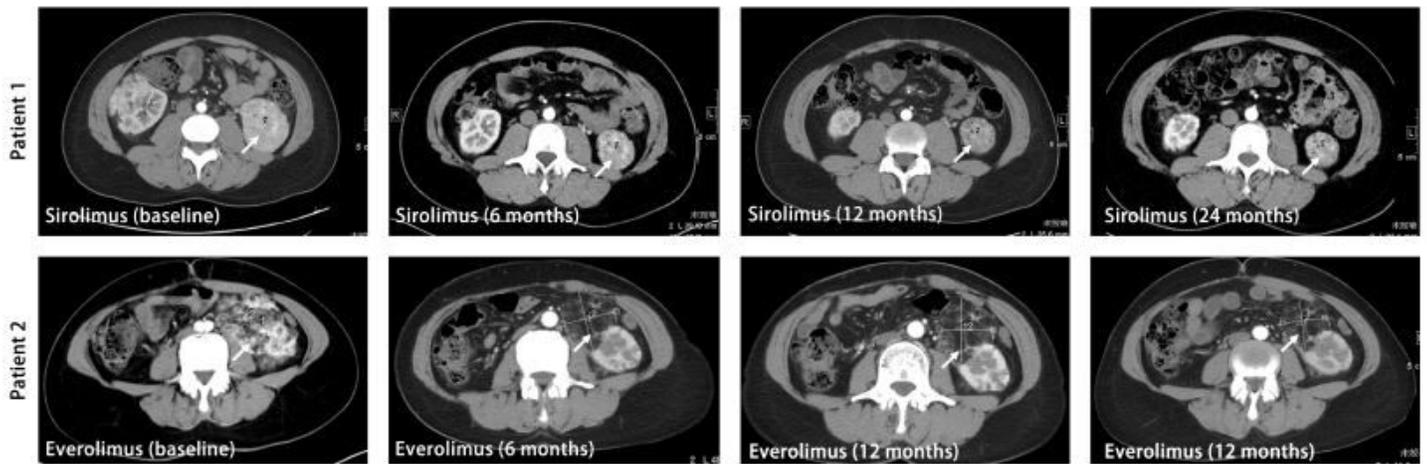
NOTE: Everolimus/Sirolimus-related adverse reactions were those adverse events that were considered to be possibly, probably, or definitely related to everolimus/sirolimus.

## Figures



**Figure 1**

Change in target AML volume. (A) Proportions of patients treated with everolimus/sirolimus with a partial response or complete clinical response in target SML lesions per physician's global assessment at 3, 6, 12 and 24 months; (B) Best percentage change from baseline in the sum of volumes of target AML lesions in everolimus patients, per central radiology review. Each bar represents one patient; (C) Best percentage change from baseline in the sum of volumes of target angiomyolipoma lesions in sirolimus patients, per central radiology review. Each bar represents one patient.



**Figure 2**

MRI imaging of two representative patients with TSC-AML in everolimus/sirolimus groups during follow-up.

## Supplementary Files

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- [title.docx](#)