

# Sirolimus Therapy after Early Cyclosporine Withdrawal Reduces the Risk for Cancer in Adult Renal Transplantation

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Sirolimus (SRL) is a mammalian target of rapamycin inhibitor that, in contrast to cyclosporine (CsA), has been shown to inhibit rather than promote cancers in experimental models. At 3 mo  $\pm$  2 wk after renal transplantation, 430 of 525 enrolled patients were randomly assigned to remain on SRL-CsA-steroids (ST) or to have CsA withdrawn and SRL troughs increased two-fold (SRL-ST). Median times to first skin and nonskin malignancies were compared between treatments using a survival analysis. Mean annualized rates of skin malignancy were calculated, and the relative risk was determined using a Poisson model. Malignancy-free survival rates for nonskin malignancies were compared using Kaplan-Meier estimates and the log-rank test. At 5 yr, the median time to a first skin carcinoma was delayed (491 versus 1126 d; log-rank test,  $P = 0.007$ ), and the risk for an event was significantly lower with SRL-ST therapy (relative risk SRL-ST to SRL-CsA-ST 0.346; 95% confidence interval 0.227 to 0.526;  $P < 0.001$ , intention-to-treat analysis). The relative risks for both basal and squamous cell carcinomas were significantly reduced. Kaplan-Meier estimates of nonskin cancer were 9.6 versus 4.0% (SRL-CsA-ST versus SRL-ST;  $P = 0.032$ , intention-to-treat analysis). Nonskin cancers included those of the lung, larynx, oropharynx, kidney, gastrointestinal tract, prostate, breast, thyroid, and cervix as well as glioma, liposarcoma, astrocytoma, leukemia, lymphoma, and Kaposi's sarcoma. Patients who received SRL-based, calcineurin inhibitor-free therapy after CsA withdrawal at month 3 had a reduced incidence of both skin and nonskin malignancies at 5 yr after renal transplantation compared with those who received SRL therapy combined with CsA. Longer follow-up and additional trials are needed to confirm these promising results.

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The introduction of potent and more effective immunosuppression has improved survival in allograft recipients and permitted an improved quality of life. However, an increased risk for malignancy remains one of the main causes of morbidity and mortality for transplant recipients. To date, this risk has largely been considered to be due to overall immunosuppression as a class effect of the agents used.

Epidemiologic data from several registries are available to estimate the increased risk for malignancy after renal transplantation. One of the most complete is the Australia and New Zealand Dialysis and Transplant Registry. In the 2004 report (1), the risk for any registrable cancer (excluding nonmelanoma skin carcinoma) in renal transplant recipients was 3.12-fold that

of the matched general Australian population. Similar results have been reported by the United States Renal Data System (2); the cumulative incidences of nonmelanoma skin carcinoma and any nonskin carcinoma at 3 yr after kidney transplantation were 7.43 and 7.45%, respectively.

Berg and Otley (3) and Euvrard *et al.* (4) recently reviewed the problem of skin carcinoma in organ transplant recipients, the most common malignancy in this population. The risk is highest in transplant recipients with fair skin and a history of high exposure to ultraviolet radiation. Approximately 45% of patients in Australian studies have a first occurrence of skin carcinoma within 10 yr after transplantation, whereas patients from Holland, England, or Italy have a 10 to 15% incidence of skin carcinoma within the same period of risk. Compared with the general US population, at 3 yr after kidney transplantation, US patients have an approximately 90- and six-fold increased risk for nonmelanoma skin carcinoma and melanoma, respectively (2).

The oncogenic effects of immunosuppressive drugs generally have been attributed to an inhibition of T lymphocyte-medi-

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ated immune surveillance, but recent results suggest distinct promoting or anticancer effects of immunosuppressive drugs used in organ transplantation (5). It has been demonstrated *in vitro* that cyclosporine (CsA)-treated tumor lines acquire an invasive phenotype that is independent of the immune system of the host (6). These works suggest a cell-autonomous mechanism for cancer progression with CsA; thus, the state of immunosuppression does not fully explain malignancies that are induced by CsA.

Immunosuppressive activity is only one of the properties of the mammalian target of rapamycin (mTOR) inhibitor, sirolimus (SRL; rapamycin, Rapamune). Several enzymes along the signaling pathway that are inhibited by SRL play a role in the development and progression of different cancers (7–9). A mouse tumor transplant model has also demonstrated the protective effect of SRL compared with the tumor-promoting effect of CsA and that SRL reduced the tumor-enhancing effects of CsA when these agents were combined (10). Recently, an analysis of the kidney transplant registry of the United Network for Organ Sharing compared the risk for cancer associated with mTOR or non-mTOR-containing regimens (11). The incidence rate of any *de novo* malignancy after 963 d of exposure was 0.60% in patients who received an mTOR without CsA/tacrolimus, 0.60% with an mTOR + CsA/tacrolimus, and 1.81% with CsA/tacrolimus ( $P < 0.0001$ ); the rates for a *de novo* solid tumor were 0, 0.47, and 1.00%, respectively.

In the Rapamune Maintenance Regimen trial, CsA withdrawal at month 3 after renal transplantation followed by concentration-controlled SRL maintenance therapy was compared with a continuous combined regimen of SRL and CsA. As we have described in the initial (12) and subsequent reports (13–16), this study has shown that early CsA withdrawal has resulted in lower BP, better renal function, and improved graft survival along with improved graft structure and better quality-of-life indices. We report the 5-yr malignancy data from this study and place these findings in perspective with regard to the problem of malignancy in transplant recipients.

## Materials and Methods

Approval for this randomized, open-label, multicenter trial was obtained from local ethics committees, and the study was carried out according to the Declaration of Helsinki. Details concerning study design and eligibility criteria were described fully in the report of findings at 12 mo (12); briefly, 525 primary (90%) or secondary (10%) adult recipients of renal allografts from deceased (89%) or living (11%) donors received SRL (nominally 2 mg/d; whole-blood trough levels 5 to 15 ng/ml, immunoassay), CsA (whole-blood trough levels 150 to 400 ng/ml), and steroids (ST) after transplantation. Patients with a history of malignancy within 5 yr before transplantation, other than adequately treated basal cell or squamous cell carcinoma, were excluded.

At 3 mo after transplantation, 430 patients from Europe (82.5%), Australia (10.5%), and Canada (7.0%) were randomly assigned to continue SRL-CsA-ST ( $n = 215$ ) or have CsA eliminated (SRL-ST,  $n = 215$ ), and SRL troughs increased approximately two-fold to 20 to 30 ng/ml during year 1, then decreased to 15 to 25 ng/ml thereafter. Overall, there were no differences in demographic characteristics between randomized treatment groups (12). A total of 94.5% of the recipients were of white ethnic origin, reflecting the ethnic composition of countries in

which the trial was conducted. On the basis of the month 36 and cumulative data available at that time (13), the protocol was amended to discontinue protocol-assigned treatment in the SRL-CsA-ST group. This amendment began affecting the discontinuation rate beginning at the month 48 visit. All patients were followed on an intent-to-treat (ITT) basis through 5 yr after transplantation.

The incidence of malignancy was a protocol-defined secondary end point, and these events were recorded on specific case report form pages. In addition, all malignancies were considered to be serious adverse events and therefore were to be reported to the sponsor (Wyeth Research, Collegeville, PA) within 1 business day of learning of the event. Narratives were requested for all patients who had a malignancy. Any malignancy was to be reported through 5 yr after transplantation, even if the patient discontinued from protocol-assigned therapy. Rates of loss to follow-up for patient survival and malignancy were 2.8 *versus* 2.3% at 3 yr and 21.4 *versus* 12.1% at 5 yr, SRL-CsA-ST *versus* SRL-ST, respectively.

Incidences of malignancy were contrasted using a  $\chi^2$  test. Median times to first malignancy were compared between treatment groups for both skin and nonskin malignancies using a survival analysis of patients with a malignancy. Malignancy-free survival was compared using the Kaplan-Meier method and the log-rank test; the population for this analysis was all patients at risk. Because skin cancers can be recurrent events, treatment groups were compared further using a suitable approach for count data (17). The mean annualized rates of skin malignancy were calculated, and the relative risk was determined using a zero-inflated Poisson model. For this analysis, the Napierian logarithm of exposure over which events were observed for each patient was included in the model as an offset variable.

These analyses were performed both by on-therapy events and ITT events, which includes events that occurred after the patient discontinued from protocol-assigned therapy. For skin malignancy, analyses were performed for any skin carcinoma, for basal cell carcinomas (BCC), and for squamous cell carcinomas (SCC). The category “any skin carcinoma” included BCC, SCC, melanoma, Bowen’s disease, and any unspecified skin carcinoma. Analyses of BCC and SCC required that these terms be specified. Each lesion was counted as a separate event, including multiple lesions reported at the same visit. For example, a BCC of the cheek, a BCC of the scalp, and an SCC of the ear that were reported on the same day counted as three separate events. Analyses for any nonskin malignancy were based on the first occurrence of any nonskin carcinoma, regardless of whether the patient had a previous skin carcinoma. Kaposi’s sarcoma was included as a nonskin cancer.

## Results

### Skin Malignancy

On-therapy and ITT analyses of any skin carcinoma are given in Table 1. The Kaplan-Meier plot of the time to a first event, along with the cumulative number of events over time for the on-therapy and ITT analyses, is illustrated in Figures 1 and 2, respectively. For the analyses of on-therapy skin carcinoma, neither the incidence of patients with an event ( $P = 0.093$ ) nor the difference in event-free survival (log-rank test,  $P = 0.055$ ) attained statistical significance. Nonetheless, the mean annualized rate was significantly lower ( $P < 0.001$ ) and the median time to the first event was significantly longer (401.5 *versus* 1248.5 d; log-rank test,  $P = 0.021$ ) in the SRL-ST group. For the ITT analysis, there was no difference in the incidence of patients with a skin malignancy ( $P = 0.597$ ) or in event-free survival (log-rank test,  $P = 0.459$ ). However, the difference in

Table 1. Number (%) of patients with any skin malignancy analyzed by on-therapy events and ITT events (5 yr)<sup>a</sup>

Analyses	SRL-CsA-ST (n = 215)	SRL-ST (n = 215)	Relative Risk SRL-CsA-ST to SRL-ST (95% CI)	P Value
<b>On-therapy</b>				
patients with malignancy (n [%])	16 (7.44)	8 (3.72)		0.093 <sup>d</sup>
no. of malignancies	80	24		
mean annualized rate (events/1000 patients per yr)	151.6	22.1	0.343 (0.205 to 0.574)	<0.001 <sup>e</sup>
time to first malignancy <sup>b</sup> (d; median [95% CI])	401.5 (167 to 682)	1248.5 (461 to 1459)		0.021 <sup>f</sup>
malignancy-free survival, <sup>c</sup> Kaplan-Meier estimates (%)	90.30	93.96		0.055 <sup>f</sup>
<b>ITT</b>				
patients with malignancy (n [%])	19 (8.84)	16 (7.44)		0.597 <sup>d</sup>
no. of malignancies	109	39		
mean annualized rate (events/1000 patients per yr)	107.7	35.8	0.346 (0.227 to 0.526)	<0.001 <sup>e</sup>
time to first malignancy <sup>b</sup> (d; median [95% CI])	491 (233 to 897)	1126 (629 to 1459)		0.007 <sup>f</sup>
malignancy-free survival, <sup>c</sup> Kaplan-Meier estimates (%)	90.57	91.68		0.459 <sup>f</sup>

<sup>a</sup>ITT, intention-to-treat; SRL-CsA-ST, sirolimus, cyclosporine A, and steroids; CI, confidence interval.

<sup>b</sup>Includes only patients with a malignancy.

<sup>c</sup>Includes all patients.

<sup>d</sup> $\chi^2$  test.

<sup>e</sup>Zero-inflated Poisson model.

<sup>f</sup>Log-rank test.

median time to an event among patients with a skin malignancy (491 *versus* 1126 d; log-rank test,  $P = 0.007$ ) was significantly longer with SRL-ST, and the risk for an event (relative risk 0.346; 95% confidence interval 0.227 to 0.556;  $P < 0.001$ ) remained significantly lower with SRL-ST compared with SRL-CsA-ST.

The difference in the number of patients with SCC was not statistically significant in any of the analyses (Table 2). However, the number of events was 29 *versus* nine and 41 *versus* 13, SRL-CsA-ST *versus* SRL-ST, for the on-therapy ( $P = 0.004$ ) and ITT analyses ( $P < 0.001$ ), respectively, and the relative risk for an SCC was significantly higher in SRL-CsA-ST group for both analyses. The number of patients with BCC was significantly lower with SRL-ST for the on-therapy analysis but not for the ITT analysis (Table 3). For both analyses, median time to a first event among patients with a BCC was significantly shorter for SRL-CsA-ST. Event-free survival was significantly better with SRL-ST for the on-therapy but not the ITT analysis. The relative risk for having a BCC was reduced in both analyses, but the difference reached statistical significance only for the ITT analysis.

There was one melanoma reported in each treatment group. BCC and malignant skin melanoma were diagnosed on day 312 in an SRL-CsA-ST patient who continued on treatment until day 743; this patient subsequently died of a grade II astrocytoma of the brain on study day 1568. Malignant skin melanoma

was diagnosed on day 1281 in one SRL-ST patient who completed the study on protocol-assigned therapy.

#### Nonskin Malignancy

Nonskin cancers included those of the lung (four *versus* one, SRL-CsA-ST *versus* SRL-ST), larynx (one *versus* zero), oropharynx (one *versus* zero), kidney (three *versus* zero), gastrointestinal tract (two *versus* one), prostate (one *versus* zero), breast (one *versus* one), thyroid (zero *versus* one), and cervix (zero *versus* one), as well as glioma (zero *versus* one), liposarcoma (zero *versus* one), astrocytoma (one *versus* zero), leukemia (one *versus* zero), lymphoma (three *versus* one), and Kaposi's sarcoma (zero *versus* one). One SRL-ST patient had both breast and cervical cancers.

Table 4 provides the on-therapy and ITT analyses of the nonskin cancers. The Kaplan-Meier plots of the time to a first event over time for these two analyses are illustrated in Figure 3. The difference between treatments was statistically significant in the ITT analysis (8.4% SRL-CsA-ST *versus* 3.7% SRL-ST,  $\chi^2 P = 0.043$ ; Kaplan-Meier estimates 9.6% SRL-CsA-ST *versus* 4.0% SRL-ST, log-rank  $P = 0.032$ ); this difference was not statistically significant for the on-therapy analysis. Of note, during the fifth year of the study, there were six nonskin malignancies in the SRL-CsA-ST group and two in the SRL-ST group.

Seven randomly assigned patients died of their cancer: Five

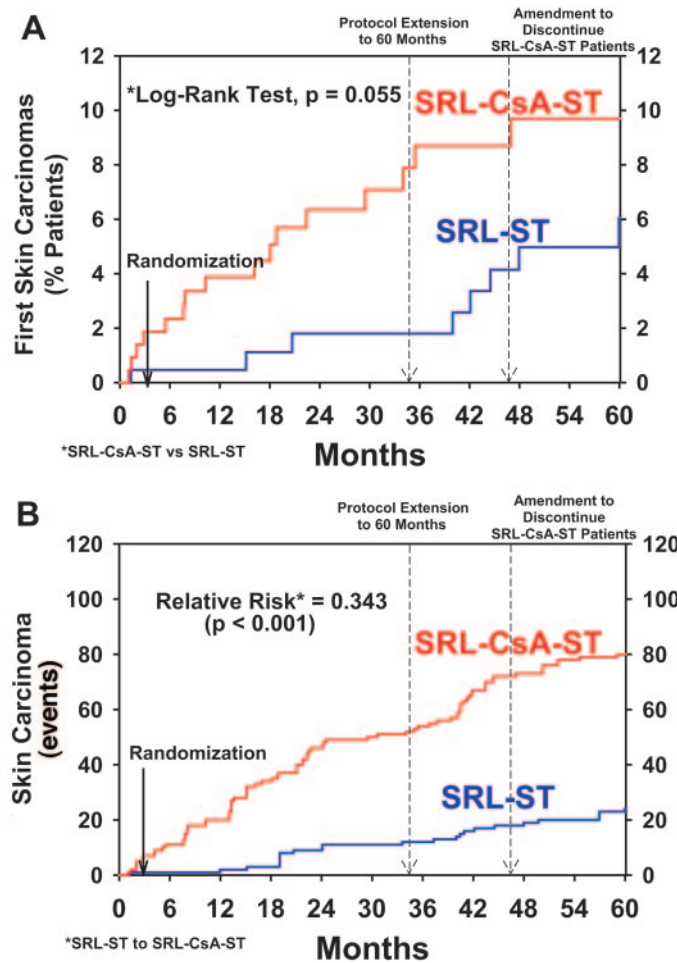


Figure 1. On-therapy analysis of any skin carcinoma. (A) Kaplan-Meier plot of time to first skin carcinoma. (B) Cumulative number of skin carcinomas.

in the SRL-CsA-ST group (three of lung cancer, one of lymphoma, and one of a metastatic skin carcinoma, astrocytoma) and two in the SRL-ST group (one of lung cancer and one of liposarcoma). Four other randomly assigned patients with malignancy died during the study, but the reason was not related to their cancer: Two patients in the SRL-CsA-ST group (one of sepsis and one of myocardial infarction, 35 and 354 d, respectively, after their malignancy was diagnosed) and two in the SRL-ST group (one of cardiac arrest and one of unknown origin, 112 and 546 d, respectively, after their malignancy was diagnosed).

## Discussion

An important goal in renal transplantation research is to identify the balance between the levels of immunosuppression necessary to prevent rejection and conserve renal function from those that contribute to the increased risk for cancer. On the basis of their pharmacologic profile, mTOR inhibitors such as SRL may be unique in this regard when compared with the calcineurin inhibitors (CNI) CsA and tacrolimus. mTOR inhibitors have considerable promise in the treatment of cancers;

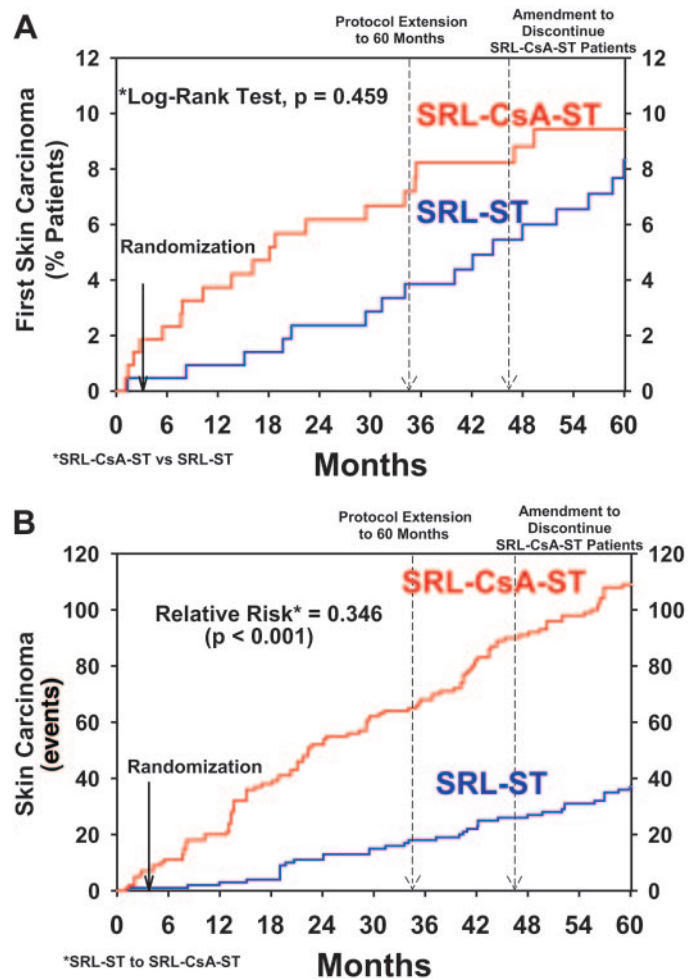


Figure 2. Intention-to-treat analysis of any skin carcinoma. (A) Kaplan-Meier plot of time to first skin carcinoma. (B) Cumulative number of skin carcinomas.

however, treating existing tumors and preventing cancer occurrence in patients who are at risk as a result of predisposing factors and the introduction of immunosuppression are two different issues.

It is unclear whether SRL has the capacity to prevent immortalization of cancer cells (*e.g.*, by preventing mutations), but it may be effective at preventing their transformation and eventual growth into malignant tumors. Koehl *et al.* (9) recently reviewed the mechanistic reasons that mTOR inhibitors such as SRL could be effective in suppressing the immune system and preventing rejection while at the same time reducing the occurrence of cancer in transplant recipients. Thus, although it is highly unlikely that tumor occurrence would be completely prevented over time, there is a reasonable expectation that SRL could delay the appearance or decrease the frequency (*e.g.*, multiple skin cancers) of malignancy, particularly when compared with more oncogenic immunosuppressive regimens.

Measuring any difference in cancer incidence between therapies requires sufficient follow-up and is challenging given the

Table 2. Number (%) of patients with any squamous cell carcinoma analyzed by on-therapy events and ITT events (5 yr)

Analyses	SRL-CsA-ST ( <i>n</i> = 215)	SRL-ST ( <i>n</i> = 215)	Relative Risk SRL-CsA-ST to SRL-ST (95% CI)	<i>P</i> Value
<b>On-therapy</b>				
patients with malignancy ( <i>n</i> [%])	6 (2.79)	4 (1.86)		0.522 <sup>c</sup>
no. of malignancies	29	9		
mean annualized rate (events/1000 patients per yr)	33.5	8.5	0.276 (0.116 to 0.656)	0.004 <sup>d</sup>
time to first malignancy <sup>a</sup> (d; median [95% CI])	606.5 (233 to 679)	604.0 (461 to 1459)		0.604 <sup>e</sup>
malignancy-free survival, <sup>b</sup> Kaplan-Meier estimates (%)	96.29	97.17		0.536 <sup>e</sup>
<b>ITT</b>				
patients with malignancy ( <i>n</i> [%])	7 (3.26)	7 (3.26)		1.000 <sup>c</sup>
no. of malignancies	41	13		
mean annualized rate (events/1000 patients per yr)	41.20	14.87	0.293 (0.152 to 0.562)	<0.001 <sup>d</sup>
time to first malignancy <sup>a</sup> (d; median [95% CI])	641 (233 to 820)	896 (579 to 1459)		0.171 <sup>e</sup>
malignancy-free survival, <sup>b</sup> Kaplan-Meier estimates (%)	96.59	96.13		0.865 <sup>e</sup>

<sup>a</sup>Includes only patients with a malignancy.

<sup>b</sup>Includes all patients.

<sup>c</sup> $\chi^2$  test.

<sup>d</sup>Zero-inflated Poisson model.

<sup>e</sup>Log-rank test.

complex and heterogeneous nature of cancer and that patients can change treatments during the course of a 5-yr study. Primary features of the analyses in this report are (1) the differentiation of skin and nonskin cancers and (2) the multiplicity of analyses including on-therapy and ITT.

Skin carcinomas such as Bowen's disease, BCC, SCC, and melanoma share common risk factors such as a fair complexion, light hair and eyes, and total exposure to ultraviolet radiation. The risks factors are usually temporally far removed from the first appearance of a skin carcinoma, in that excessive exposure to ultraviolet light and sunburns during childhood can result in an increased risk for skin carcinomas beginning in the fifth or sixth decades of life. In this trial, the incidence of skin carcinoma was 21.3% in Australian patients and 6.7% overall in European and Canadian patients. However, because Europe contributed 82.5% of the randomly assigned patients compared with 10.5% from Australia and 7.0% from Canada, the majority of patients with skin carcinoma in this trial were European.

Introduction of immunosuppression in renal transplantation rapidly increases the incidences of skin carcinomas such as BCC and SCC from 10-fold and 65- to 250-fold, respectively, well above the rate for the matched nontransplant general population (3,4). They are also recurrent events that are treated by excision or other methods of physical removal. Although the

greatest risk with skin carcinomas is the possibility of nonskin metastases, the frequency and the number of events are important elements of the morbidity. A patient with 27 lesions, the maximum number observed in this study, should be assessed differently from a patient with a single lesion. Accordingly, in addition to comparing the number of patients with an event and the time to the first event, we also determined the mean annualized rate of skin malignancies (number of events  $\times$  365 d/length of exposure to the risk) and compared the groups using a zero-inflated Poisson model. This approach is appropriate for comparing the rates of multiple events and is commonly used in other areas of clinical research (18).

With regard to any skin malignancy, there were fewer lesions with CsA withdrawal (SRL-ST), the mean annualized rates were lower, and the relative risk for having a skin cancer was significantly lower ( $P < 0.001$  for both the on-therapy and ITT analyses). Moreover, the median time to a first skin malignancy was significantly later in SRL-ST patients. These findings were observed even though the number of patients with a skin malignancy and the event-free survivals were not significantly different between groups for any of the analyses. A comparison of the time-to-event curves shows that there is a trend toward convergence of time-to-event curves for the ITT analyses, suggesting that patients who discontinue SRL-ST and return to CNI-based therapy return to a

Table 3. Number (%) of patients with any basal cell carcinoma analyzed by on-therapy events and ITT events (5 yr)

Analyses	SRL-CsA-ST (n = 215)	SRL-ST (n = 215)	Relative Risk SRL-CsA-ST to SRL-ST (95% CI)	P Value
<b>On-therapy</b>				
patients with malignancy (n [%])	12 (5.58)	4 (1.86)		0.042 <sup>c</sup>
no. of malignancies	36	13		
mean annualized rate (events/1000 patients per yr)	89.9	11.9	0.561 (0.267 to 1.178)	0.126 <sup>d</sup>
time to first malignancy <sup>a</sup> (d; median [95% CI])	235 (86 to 491)	1474 (40 to 1824)		0.022 <sup>e</sup>
malignancy-free survival <sup>b</sup> , Kaplan-Meier estimates (%)	93.45	96.81		0.017 <sup>e</sup>
<b>ITT</b>				
patients with malignancy (n [%])	14 (6.51)	10 (4.65)		0.401 <sup>c</sup>
no. of malignancies	49	19		
mean annualized rate (events/1000 patients per yr)	49.01	18.18	0.413 (0.216 to 0.791)	0.008 <sup>d</sup>
time to first malignancy <sup>a</sup> (d; median [95% CI])	274.5 (86 to 550)	1126 (599 to 1732)		0.003 <sup>e</sup>
malignancy-free survival <sup>b</sup> , Kaplan-Meier estimates (%)	93.28	94.74		0.316 <sup>e</sup>

<sup>a</sup>Includes only patients with a malignancy.

<sup>b</sup>Includes all patients.

<sup>c</sup> $\chi^2$  test.

<sup>d</sup>Zero-inflated Poisson model.

<sup>e</sup>Log-rank test.

Table 4. Number (%) of patients with any nonskin malignancy analyzed by on-therapy events and ITT events (5 yr)

Analyses	SRL-CsA-ST (n = 215)	SRL-ST (n = 215)	P Value
<b>On-therapy</b>			
nonskin malignancies (n [%])	10 (4.65)	4 (1.86)	0.103 <sup>c</sup>
time to first malignancy <sup>a</sup> (d; median [95% CI])	638.0 (461 to 1149)	407.5 (242 to 1544)	0.644 <sup>d</sup>
malignancy-free survival <sup>b</sup> , Kaplan-Meier estimates (%)	92.62	97.36	0.094 <sup>d</sup>
<b>ITT</b>			
nonskin malignancies (n [%])	18 (8.37)	8 (3.72)	0.043 <sup>c</sup>
time to first malignancy <sup>a</sup> (d; median [95% CI])	668.0 (538 to 1511)	774.5 (267 to 1544)	0.625 <sup>d</sup>
malignancy-free survival <sup>b</sup> , Kaplan-Meier estimates (%)	90.38	95.99	0.032 <sup>d</sup>

<sup>a</sup>Includes only patients with a malignancy.

<sup>b</sup>Includes all patients.

<sup>c</sup> $\chi^2$  test.

<sup>d</sup>Log-rank test.

higher risk for skin carcinoma within a few months. Consequently, data from patients who had CsA withdrawn in this study showed that there was a delay in the appearance of the first skin carcinoma and reduction in the total number of carcinomas rather than a significant reduction in the number of patients with at least

one skin carcinoma. However, one could speculate that the difference in the number of patients with a skin cancer in each treatment group would also become significantly different if patients had remained on their original protocol-assigned therapy through the entire 5 yr.

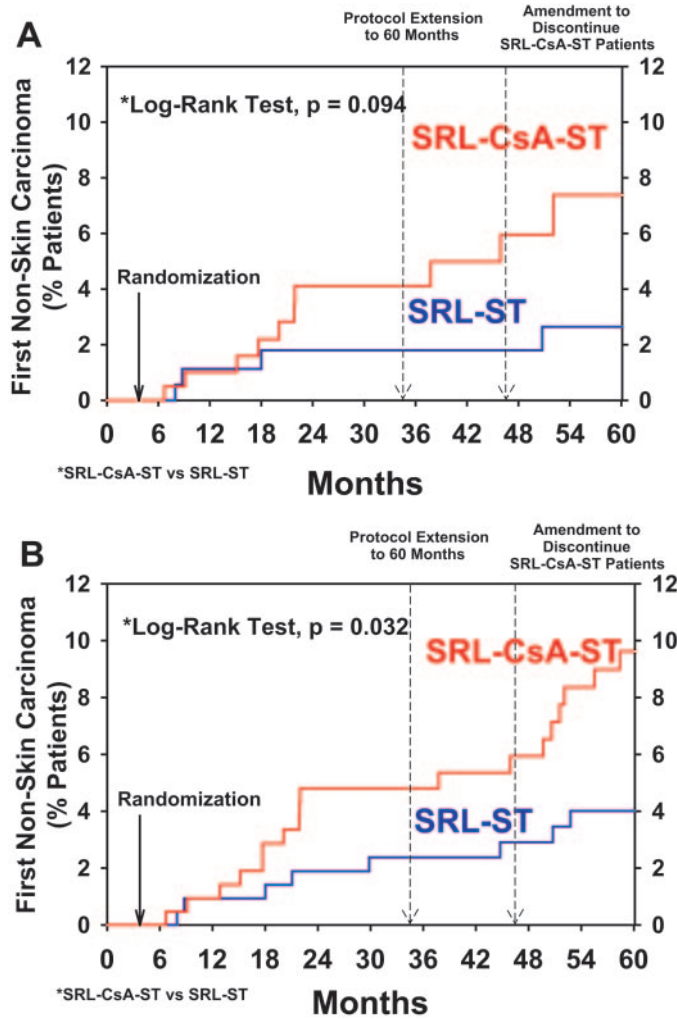


Figure 3. Kaplan-Meier plots of time to nonskin malignancies. (A) On-therapy. (B) Intention-to-treat.

Independent analysis of BCC and SCC indicated that SRL-based, CNI-free immunosuppression after CsA withdrawal had a favorable impact on the mean annualized rate for both of these events, with a pronounced effect in delaying the median time to first occurrence of a BCC. It can also be noted for SCC that the mean annualized rate was higher in both groups in the ITT than in the on-therapy analysis, suggesting that discontinuation from either group increased the rate of SCC. On the contrary, the mean annualized rate of BCC was higher in the ITT than in the on-therapy analysis for SRL-ST but lower with SRL-Csa-ST, possibly suggesting that discontinuing from SRL-ST but not SRL-Csa-ST increased the rate of BCC as well. Regardless of whether the analysis was on-therapy or ITT, the BCC:SCC event ratio was approximately 1.2 for SRL-Csa-ST and 1.4 for SRL-ST. Most authors (4), although not all (19), have reported that the higher BCC:SCC ratio observed in the general population is reversed in renal transplant recipients. That both treatment groups received SRL could also have affected the BCC:SCC ratio, compared with previous reports based on regimens that did not include SRL.

Primary and metastatic nonskin malignancies were varied (lung, larynx, oropharynx, kidney, gastrointestinal tract, prostate, breast, thyroid, and cervix as well as glioma, liposarcoma, astrocytoma, leukemia, lymphoma, and Kaposi's sarcoma). The only Kaposi's sarcoma reported in this trial occurred in an SRL-ST patient, 756 d after the patient discontinued SRL on day 152 for increased creatinine. SRL therapy has been shown to produce remissions of Kaposi's syndrome in renal transplant recipients who converted to SRL (20,21).

For nonskin malignancies, the difference between treatments approached statistical significance in the on-therapy analysis, and it was statistically significantly different in favor of SRL-ST therapy for the ITT analysis (8.4% SRL-Csa-ST versus 3.7% SRL-ST,  $\chi^2 P = 0.043$ ; Kaplan-Meier estimates 9.6% SRL-Csa-ST versus 4.0% SRL-ST, log-rank  $P = 0.032$ ). The time-to-event curves across the on-therapy and ITT analyses were comparable without the same trend to convergence in the ITT analyses observed for skin carcinomas. There may be an increased risk for developing a nonskin cancer when a patient discontinues an SRL-based, CNI-free regimen for a CNI-based regimen, but this was not detected in this trial. Importantly, >50% of SRL-ST patients completed 5 yr of therapy (see Figure 4).

It should be emphasized that both treatment groups contained SRL; the difference was that SRL-Csa-ST patients also received standard- or near-standard-dose CsA therapy and the SRL-ST patients had approximately two-fold higher SRL trough levels. Experimentally, tumor growth and metastases are accelerated by CsA or tacrolimus and are reduced or halted by SRL (10,22). Moreover, in mice that bore B16 melanoma and received an allogeneic heart transplant, it has been shown that tumor growth responded similarly to SRL plus CsA and to sirolimus alone, suggesting that SRL may oppose the tumor-enhancing effect of CsA (10). Clinical evidence that SRL can reduce the incidence of malignancy even in the presence of CNI can be found in the United Network for Organ Sharing data-

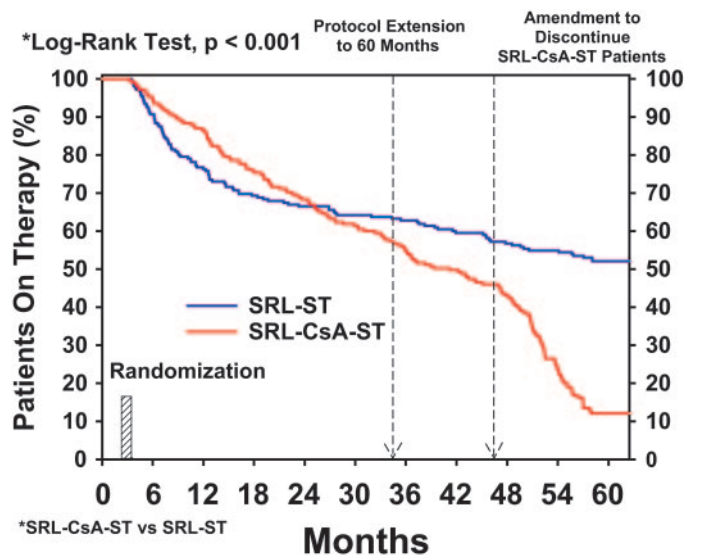


Figure 4. Patients who remained on therapy.

base analysis by Kauffman *et al.* (11); mTOR inhibitors either with or without a CNI reduced the relative risk for a *de novo* malignancy. This trial suggests that there is a graded effect, with early CsA withdrawal followed by increased SRL exposure resulting in significantly lower rates of malignancy than a continuous combined regimen of SRL with CsA. Therefore, one may also speculate that a 5-yr study comparing an SRL-based, CNI-free regimen with a CNI-based, SRL-free regimen may have produced an even greater difference in the incidence of cancers than that observed in this trial.

## Conclusion

Renal transplant recipients have a higher risk for developing cancer as compared with the general population. The results from this study are in agreement with previous reports associating this risk with immunosuppressive therapies. However, when compared with a continuous regimen of SRL and CsA, SRL-based, CNI-free therapy after CsA withdrawal at month 3 significantly reduced the risk for skin and nonskin cancer at 5 yr after renal transplantation. SRL-based therapy may offer patients an important opportunity to reduce their risk for an all too frequent cause of morbidity and mortality after successful renal replacement therapy with kidney transplantation. Longer follow-up and additional trials are needed to confirm these promising results.

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