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**Management of Kaposi Sarcoma after Solid Organ Transplantation:  
a European Retrospective Study**

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61    participated in data collection and critically reviewed the manuscript;

62    RP constructed the statistical design and performed data analysis;

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## ABSTRACT

**Background:** Systemic therapeutic management of post-transplant Kaposi sarcoma (KS) is mainly based on 3 axes: reduction of immunosuppression, conversion to mammalian target of rapamycin (mTOR) inhibitors and/or chemotherapy.

**Objective:** To obtain an overview of clinical strategies about the current treatment of KS.

**Methods:** We conducted a multicenter retrospective cohort study including 145 solid organ transplant recipients diagnosed with KS between 1985 and 2011 to collect data regarding first-line treatment and response at 6 months.

**Results:** Ninety five percent, 28% and 16% of patients had reduction of immunosuppression, conversion to mTOR inhibitor and chemotherapy, respectively. Patients treated with chemotherapy or mTOR inhibitor conversion were more likely to have visceral KS. Overall, 83% of patients had response at 6 months including 40% complete responses (CR).

**Limitations:** The retrospective design of the study.

**Conclusion:** Currently available therapeutic options seem to be effective to control KS in a majority of patients. Tapering down the immunosuppressive regimen remains the cornerstone of KS management.

## INTRODUCTION

As graft maintenance requires continuous immunosuppressive therapy, solid organ transplant recipients (OTRs) are at high risk of developing various types of cancer, particularly those associated with viral infections<sup>1</sup>. Kaposi sarcoma(KS) is a lymphatic endothelium-derived tumor associated with human herpes virus type 8(HHV-8) promoted by immunosuppression. Most cases of post-transplant KS arise as a result of HHV-8 reactivation triggered by drug-induced immunosuppression<sup>2,3</sup>, resulting in a 200-fold higher risk in OTRs than in the general population<sup>4</sup>. In the 1990s, mortality of KS was high, estimated to be 57% in patients with visceral extension of the disease<sup>5,6</sup>. Since then, post-transplant KS management has largely changed, with greater emphasis on minimization of immunosuppression rather than use of chemotherapy, but current mortality rates from post-transplant KS are unknown. Therapeutic management is still a challenge, as it requires both controlling the disease whilst maintaining graft function.

Reduction of immunosuppression(IS) is an effective therapeutic option to reduce occurrence of malignancies in OTRs<sup>7</sup>, but is limited by the risk of graft rejection. In KS, remission after decrease of IS alone ranged from 30% to 50% in retrospective series<sup>6,8</sup>. Moreover, all immunosuppressive drugs do not carry the same risk of malignancies; particularly, mammalian target of rapamycin inhibitors(mTORi) have both immunosuppressive effects and direct antineoplastic effects<sup>9</sup>. Sirolimus has been associated with reduced occurrence of skin cancers, including KS, and to a lesser extent non skin malignancies<sup>10-12</sup>.

Therapy for post-transplant KS has changed over the past two decades. In 2005, conversion to mTORi was shown to have a therapeutic effect: conversion from calcineurin inhibitors (CNI) and/or purine antagonists to sirolimus induced responses in 72-100% of patients<sup>13,14</sup>. However, relapse and the apparent absence of remission in patients with visceral KS were reported in a significant proportion of patients treated with sirolimus<sup>14,15</sup>. Chemotherapy is

usually required in patients with visceral involvement or rapidly evolving KS and their use has been best evaluated in AIDS-related KS<sup>16,17</sup>. The therapeutic armamentarium against post-transplant KS is now based upon 3 axes –reduction of IS, conversion to mTORi and use of chemotherapy. However, neither comparative prospective trials nor retrospective studies have been conducted in post-transplant KS, and no consensus guidelines are available. We conducted a retrospective study amongst expert European centers belonging to the Skin Care in Organ Transplant Patients, Europe (SCOPE)network, in order to obtain an overview of the efficacy of treatment and prognosis in post-transplant KS.

## **MATERIALS AND METHODS**

### **Patients**

This multicenter retrospective study was conducted in 15 transplant centers in 6 countries (France, United Kingdom, Turkey, Belgium, Netherlands and Spain). The study was approved by Ethics Committees in each country.

Solid OTRs with a pathologically-confirmed diagnosis of post-transplant KS diagnosed between 1985 and 2011 were included. Patients with HIV were not included.

Clinical data were collected through a questionnaire completed from medical records, included demographic data, transplantation data, characteristics of KS, KS therapeutic management and response to treatment. KS extension was defined as visceral (at least one site among: lymph node, pulmonary or other visceral organ involvement) or not (for patients with cutaneous and/or mucosal only). First-line therapeutic management was defined as systemic care given in the first two months after KS diagnosis. Therapeutic options were: reduction of IS, conversion to mTORi and/or chemotherapy. Reduction of IS included dose reduction or drug withdrawal for corticosteroids, mycophenolate mofetil (MMF), azathioprine or CNI (cyclosporine, tacrolimus).

Response to KS first-line management at 6 months was classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) following the Physician Global Assessment<sup>18</sup>.

### **Statistical analyses**

Characteristics of treatment groups were compared using Fisher's exact tests, Wilcoxon rank-sum tests or Kruskal-Wallis tests. Progression-free survival (PFS) was defined as the time delay between the first therapeutic decision to first evidence of disease progression or death, whichever occurred first. Patients were otherwise censored at their last follow-up date.



Overall survival(OS) was defined as the time between KS diagnosis and death. PFS and OS were assessed using Kaplan Meier estimator. Graft loss was defined as the occurrence of a second organ transplantation or hemodialysis; the cumulative incidence of graft loss was analyzed in a competing risks framework, with death as competing event.

To account for confounding due to baseline imbalance in prognostic factors in the comparison of PFS between patients receiving mTORi to those not receiving mTORi, two approaches were used. First, inverse probability of treatment weighting(IPTW) was used to reconstruct pseudo-populations with similar baseline characteristics. Adjusted Kaplan-Meier curves were then estimated<sup>19</sup>, and a Cox model with robust variance estimator was used for comparison. Second, regression adjustment using Cox models was used. Variables used were predefined potential prognostic variables (mucosal KS, lymph node involvement, symptomatic visceral KS, CMV infection, CMV prophylaxis, HSV prophylaxis). HHV8 viral load was not used due to too many missing data. Missing covariates were handled through multiple imputation by chained equations<sup>20,21</sup>. Fifty imputed datasets were created, and analyzed separately. Results were then pooled over the imputations according to Rubin's rule.

Statistical analyses were performed using the R statistical software version 3.2(The R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

### Patient characteristics

145 patients with post-transplant KS diagnosed between February 1985 and April 2011 were enrolled (France, n=109; United-Kingdom, n=14; Turkey, n=9; Belgium, n=7; Netherlands, n=4; Spain, n=2). Ninety-one patients were diagnosed with KS after 2005, when the first study highlighting the benefits of mTORi in post-transplant KS was reported<sup>13</sup>. Baseline characteristics are summarized in **Table 1**. Seventy-six percent of patients were male, with a median age of 53 years. Most patients were kidney transplant recipients (89%).

KS developed within a median time of 17 months after transplantation (IQR,9-38). Prior history of primary HHV-8 infection was reported in two patients only. All patients were receiving immunosuppressive therapies, including a CNI for 92%. Four patients had already been receiving mTOR inhibitor therapy before KS diagnosis.

Fifty-one percent of patients had visceral KS, which was symptomatic for 20 patients (14%). Pulmonary KS was reported in 20% of patients.

### First-line therapeutic management

First-line therapeutic management was highly variable between patients (**Figure 1**). Nevertheless, most patients shared the common feature of having reduction of IS (95%), which included dose reduction or drug withdrawal for CNI, MMF, azathioprine or corticosteroids. Conversion to mTORi was performed in 28% of patients, mostly in association with reduction of other drugs. Among patients whose KS was diagnosed after 2005 (n=91), 67% had conversion to mTORi, vs. 3% among patients before 2005.

Chemotherapy, usually required for severe KS<sup>22,23</sup>, was used as first line for 23 patients (16%), in addition to reduction of IS (n=12, 8%) or conversion to mTORi (n=10, 7%). Cytotoxic agents included liposomal doxorubicin (n=9), bleomycin monotherapy (n=4),

ABV (adriamycin, bleomycin, vinblastine, n=5), vinblastine (n=2), paclitaxel (n=1), bleomycin and vinblastine (n=1) and vindesine (n=1).

In addition, local treatments were reported in 15 patients (surgery, n=8; radiotherapy, n=5; imiquimod, n=2).

### **Characteristics associated with first-line therapeutic management of KS**

Given that 95% of patients had reduction of IS, we defined 4 groups of patients among the therapeutic options, i.e. conversion to mTORi and use chemotherapy. Specifically, Group 1 (n=92), no mTORi conversion, no chemotherapy; Group 2 (n=13), no mTORi conversion, with chemotherapy; Group 3 (n=30), mTORi conversion, no chemotherapy; Group 4 (n=10), mTORi conversion, with chemotherapy. Group 1 included almost exclusively patients with reduction of IS (97%), which included dose reduction or withdrawal for CNI (n=54), AZA (n=39), MMF (n=11) and/or corticosteroids (n=16). Characteristics of patients in these four subgroups are summarized in **Table 2**.

Some characteristics related to KS extent were significantly different between groups. The proportion of patients having symptomatic visceral KS or lymph node involvement was significantly higher in Group 4 than in Groups 1, 2, 3 ( $P<0.0001$ ). Fifty-five percent of patients with symptomatic visceral KS vs. 10% of patients without symptomatic visceral KS, were treated with chemotherapy as first line treatment. Thus, Group 4 was mostly composed of patients with visceral KS: 67% and 90% of patients had symptomatic visceral KS and lymph node involvement, respectively, vs. 6% and 20% of patients in Group 1. Irrespective of chemotherapy use, patients who received mTORi also had more advanced disease, with a higher proportion of symptomatic visceral lesions ( $P=0.027$ ), more lymph node involvement ( $P=0.051$ ) and more visceral lesions ( $P=0.035$ ).

## **KS response to first-line therapeutic management**

Among 137 evaluable patients, 83% had response to the treatment at 6 months, including 40% with CR and 43% with PR (**Figure 2**). CR occurred more frequently in patients without visceral involvement (47%) than in patients with visceral disease (30%), while PR was more frequent in patients with visceral involvement (51% vs. 31%). 11% of patients experienced PD at 6 months. For patients who had visceral disease (n=73), 55 were treated with only reduced IS or mTORi and 18 received chemotherapy. 71 patients were evaluable for response. Of the 18 patients treated with chemotherapy, 5 (28%) had a complete response, 8 (44%) had a partial response. Among the 53 evaluable patients with visceral disease not treated with chemotherapy, 17 (32%) had PR and 29 (55%) had CR.

The two most used therapeutic options, which were reduction of IS (97% of patients in Group 1), and reduction of IS associated with conversion to mTORi (90% of patients in Group 3), had a similar response rate of 86%. Conversion to mTORi induced 17% CR and 69% PR. However, patients who did not receive mTORi achieved more CR ( $P=0.0002$ ) but not more overall responses (CR+PR) (**Figure 2**).

Bearing in mind that patients' characteristics were different between treatment groups (**Table 2**), response rates were similar with chemotherapy. In patients treated with conversion to mTORi, 17% and 69% had CR and PR respectively, while those who had additional chemotherapy had 10% of CR and 70% of PR. Among patients without conversion to mTORi, response rates were lower for those treated with chemotherapy (62% vs. 86%).

Patients with KS relapse or who progressed upon first line treatment (n=52) were treated with chemotherapy (n=25, 52%), additional reduction of immunosuppression (n=24, 46%) and/or switch to mTORi (15%).

## **Survival**

The median follow-up time was 91 months from KS diagnosis (7.6 years, range 1 to 276 months). During follow-up, 37 patients died, including 4 deaths due to KS (3%) and 3 of unknown causes. OS was 82% at 5 years(95%CI:75-89%), and 64% at 10 years(95%CI:54-75%). OS was not related to KS extent at diagnosis.

Differences in PFS were found between the four Groups ( $P=0.0008$ ) (**Figure 3B**), with better PFS in Group 1 patients. However, treatment groups differed according to patient baseline characteristics, specifically the extent of disease (**Table 2**). To account for this confounding due to baseline imbalance in potential prognostic factors, IPTW estimators and regression adjustment were used to compare PFS between patients receiving mTORi or not (but not chemotherapy as this group was too small sample size). Results were similar for unadjusted, IPTW and adjusted analyses, with hazard ratios(HRs) for mTORi vs. no mTORi of 2.18(95%CI:1.18-4.05), 2.22(1.23-4.03) and 2.45(1.29-4.645), respectively (**Figure 3**).

#### **Graft survival**

Similar analyses were performed to study the risk of graft failure related to KS management. Graft loss occurred in 34 patients. Across the 4 groups, the cumulative incidence of graft loss was not different ( $P=0.99$ , Gray test). Using IPTW, the HR of graft rejection for mTORi vs. no mTORi was not significantly increased nor decreased (HR 0.69; 95% CI: 0.20-2.34).

## DISCUSSION

In this study, patient data from 15 centers across Europe were pooled to obtain an overview of post-transplant KS management and responses to treatment. Treatment was mostly based on IS reduction and conversion to mTORi, inducing response in more than 80% of patients. KS-related deaths rarely occurred, suggesting that KS can be effectively controlled.

mTORi were included in the armamentarium of immunosuppressive drugs since 2000<sup>24</sup>. In 2005, Stallone and colleagues demonstrated that mTOR inhibitors induced CR in 100% of 15 patients with post-transplant KS<sup>13</sup>. This effective strategy based on CNI withdrawal and switch to mTORi was confirmed in other studies<sup>14,25–27</sup>, although Lebbé et al. reported a significant proportion of relapses (3/14 patients) and resistance in patients with visceral KS<sup>14</sup>. Switch to mTORi became part of the standard management strategy of post-transplant KS<sup>22,23</sup>. In the present study, conversion to mTORi induced responses in more than 80% of patients. However these patients -who certainly had more visceral KS-experienced fewer CRs than those who did not receive mTORi. Statistical maneuvers to adjust for important prognostic factors such as disease extent were undertaken. Despite this, the long-term risk of disease progression remained significantly higher in OTR who received mTORi.

Reduction of IS is still the cornerstone of post-transplant KS management. In this study almost all patients had minimization of IS, and 50% of CR had been achieved solely by a decrease of IS. Clinical benefits reported in mTORi conversion and/or chemotherapy groups might be partially attributable to decrease of IS. Moreover, in contrast to prospective studies, reduction of immunosuppressive therapies is highly heterogeneous in retrospective studies. Beyond the level of IS, the type of regimen also contributes to the risk of post-transplant malignancies. CNI were found to have direct oncogenic properties<sup>28–30</sup> and CNI withdrawal was associated with risk reduction of post-transplant malignancies<sup>10</sup>. Conversely, in KS there is a growing amount of evidence suggesting that mTORi have direct anti-tumor cell effects

that are independent of the immune system<sup>31,32</sup>. In contrast, everolimus was unsuccessfully tested in classic KS suggesting that immunosuppressive effects of mTORi could override its antineoplastic properties in immunocompetent patients, while this appears not to be the case in immunocompromised patients<sup>33,34</sup>.

Chemotherapy is usually required in cases of extensive or symptomatic visceral KS<sup>22</sup>. In our cohort, chemotherapy was used for advanced KS (visceral involvement and/or rapid progression) in fewer than 20% of patients. Response rates were increased in association with mTORi conversion, suggesting that in patients with visceral KS, combination of mTORi and short-term chemotherapy could be an effective strategy.

This study represents the largest case series to focus on post-transplant KS and the first to report first-line practices. The retrospective design limits detailed comparison of data as it could not be ruled out that different outcomes in treatment groups were due to unmeasured confounding factors. Screening for KS extension at diagnosis was performed upon local practices, and might be heterogeneous between centers. Missing information as KS treatment received after the first 2 months limited quantity and quality of interpretable data. For instance, data regarding the optimal time to conversion to mTORi after KS diagnosis or the total amount of corticosteroids received after KS diagnosis, which is associated with KS occurrence and outcome<sup>35</sup>, could not be studied in detail. Finally, the study population was probably heterogeneous because of the extended inclusion period, during which practices regarding immunosuppressive regimens and KS therapeutic strategy have evolved, particularly pre- and post-2005<sup>13</sup>.

This study provides insight into clinical practices in post-transplant KS management, which is based on reduction of IS in addition to conversion to mTORi, and/or chemotherapy. The signal from our data that mTORi conversion may be associated with a higher risk of progression is complicated by multiple potential confounders including KS extent, but is an

303 indication that further prospective studies are now warranted to precisely assess the long-term  
304 benefits of conversion to mTORi in the management of post-transplant KS.

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## REFERENCES

1. Schulz TF. Cancer and viral infections in immunocompromised individuals. *Int J Cancer*. 2009;125(8):1755-1763. doi:10.1002/ijc.24741
2. Francès C, Mouquet C, Marcelin AG, et al. Outcome of kidney transplant recipients with previous human herpesvirus-8 infection. *Transplantation*. 2000;69(9):1776-1779.
3. Francès C, Marcelin AG, Legendre C, et al. The impact of preexisting or acquired Kaposi sarcoma herpesvirus infection in kidney transplant recipients on morbidity and survival. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2009;9(11):2580-2586. doi:10.1111/j.1600-6143.2009.02816.x
4. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet Lond Engl*. 2007;370(9581):59-67. doi:10.1016/S0140-6736(07)61050-2
5. Farge D. Kaposi's sarcoma in organ transplant recipients. The Collaborative Transplantation Research Group of Ile de France. *Eur J Med*. 1993;2(6):339-343.
6. Penn I. Kaposi's sarcoma in transplant recipients. *Transplantation*. 1997;64(5):669-673.
7. Dantal J, Hourmant M, Cantarovich D, et al. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. *Lancet Lond Engl*. 1998;351(9103):623-628. doi:10.1016/S0140-6736(97)08496-1
8. Barete S, Calvez V, Mouquet C, et al. Clinical features and contribution of virological findings to the management of Kaposi sarcoma in organ-allograft recipients. *Arch Dermatol*. 2000;136(12):1452-1458.
9. Geissler EK, Schlitt HJ, Thomas G. mTOR, cancer and transplantation. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2008;8(11):2212-2218. doi:10.1111/j.1600-6143.2008.02391.x
10. Campistol JM, Eris J, Oberbauer R, et al. Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. *J Am Soc Nephrol JASN*. 2006;17(2):581-589. doi:10.1681/ASN.2005090993
11. Euvrard S, Morelon E, Rostaing L, et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. *N Engl J Med*. 2012;367(4):329-339. doi:10.1056/NEJMoal204166
12. Hoogendijk-van den Akker JM, Harden PN, Hoitsma AJ, et al. Two-year randomized controlled prospective trial converting treatment of stable renal transplant recipients with cutaneous invasive squamous cell carcinomas to sirolimus. *J Clin Oncol*. 2013;31(10):1317-1323. doi:10.1200/JCO.2012.45.6376
13. Stallone G, Schena A, Infante B, et al. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *N Engl J Med*. 2005;352(13):1317-1323. doi:10.1056/NEJMoal042831

- 345 14. Lebbé C, Euvrard S, Barrou B, et al. Sirolimus conversion for patients with  
346 posttransplant Kaposi's sarcoma. *Am J Transplant Off J Am Soc Transplant Am Soc*  
347 *Transpl Surg*. 2006;6(9):2164-2168. doi:10.1111/j.1600-6143.2006.01412.x
- 348 15. Monaco AP. The role of mTOR inhibitors in the management of posttransplant  
349 malignancy. *Transplantation*. 2009;87(2):157-163. doi:10.1097/TP.0b013e318193886e
- 350 16. Cianfrocca M, Lee S, Von Roenn J, et al. Randomized trial of paclitaxel versus  
351 pegylated liposomal doxorubicin for advanced human immunodeficiency virus-  
352 associated Kaposi sarcoma: evidence of symptom palliation from chemotherapy.  
353 *Cancer*. 2010;116(16):3969-3977. doi:10.1002/cncr.25362
- 354 17. Little RF, Aleman K, Kumar P, et al. Phase 2 study of pegylated liposomal doxorubicin  
355 in combination with interleukin-12 for AIDS-related Kaposi sarcoma. *Blood*.  
356 2007;110(13):4165-4171. doi:10.1182/blood-2007-06-097568
- 357 18. Pourcher V, Desnoyer A, Assoumou L, et al. Phase II Trial of Lenalidomide in HIV-  
358 Infected Patients with Previously Treated Kaposi's Sarcoma: Results of the ANRS 154  
359 Lenakap Trial. *AIDS Res Hum Retroviruses*. 2017;33(1):1-10.  
360 doi:10.1089/AID.2016.0069
- 361 19. Xie J, Liu C. Adjusted Kaplan-Meier estimator and log-rank test with inverse probability  
362 of treatment weighting for survival data. *Stat Med*. 2005;24(20):3089-3110.  
363 doi:10.1002/sim.2174
- 364 20. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and  
365 some applications. *Stat Med*. 1991;10(4):585-598.
- 366 21. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues  
367 and guidance for practice. *Stat Med*. 2011;30(4):377-399. doi:10.1002/sim.4067
- 368 22. Lebbé C, Legendre C, Francès C. Kaposi sarcoma in transplantation. *Transplant Rev*  
369 *Orlando Fla*. 2008;22(4):252-261. doi:10.1016/j.trre.2008.05.004
- 370 23. Riva G, Luppi M, Barozzi P, Forghieri F, Potenza L. How I treat HHV8/KSHV-related  
371 diseases in posttransplant patients. *Blood*. 2012;120(20):4150-4159. doi:10.1182/blood-  
372 2012-04-421412
- 373 24. Kahan BD. Efficacy of sirolimus compared with azathioprine for reduction of acute  
374 renal allograft rejection: a randomised multicentre study. The Rapamune US Study  
375 Group. *Lancet Lond Engl*. 2000;356(9225):194-202.
- 376 25. Campistol JM, Schena FP. Kaposi's sarcoma in renal transplant recipients--the impact of  
377 proliferation signal inhibitors. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc*  
378 *- Eur Ren Assoc*. 2007;22 Suppl 1:i17-22. doi:10.1093/ndt/gfm089
- 379 26. Hernández-Sierra A, Rovira J, Petit A, et al. Role of HHV-8 and mTOR pathway in  
380 post-transplant Kaposi sarcoma staging. *Transpl Int Off J Eur Soc Organ Transplant*.  
381 May 2016. doi:10.1111/tri.12800

27. Gutiérrez-Dalmau A, Sánchez-Fructuoso A, Sanz-Guajardo A, et al. Efficacy of conversion to sirolimus in posttransplantation Kaposi's sarcoma. *Transplant Proc.* 2005;37(9):3836-3838. doi:10.1016/j.transproceed.2005.10.076
28. Hojo M, Morimoto T, Maluccio M, et al. Cyclosporine induces cancer progression by a cell-autonomous mechanism. *Nature.* 1999;397(6719):530-534. doi:10.1038/17401
29. Guba M, Graeb C, Jauch K-W, Geissler EK. Pro- and anti-cancer effects of immunosuppressive agents used in organ transplantation. *Transplantation.* 2004;77(12):1777-1782.
30. Datta D, Contreras AG, Basu A, et al. Calcineurin inhibitors activate the proto-oncogene Ras and promote protumorigenic signals in renal cancer cells. *Cancer Res.* 2009;69(23):8902-8909. doi:10.1158/0008-5472.CAN-09-1404
31. Roy D, Sin S-H, Lucas A, et al. mTOR inhibitors block Kaposi sarcoma growth by inhibiting essential autocrine growth factors and tumor angiogenesis. *Cancer Res.* 2013;73(7):2235-2246. doi:10.1158/0008-5472.CAN-12-1851
32. Barozzi P, Riva G, Vallerini D, et al. Indirect antitumor effects of mammalian target of rapamycin inhibitors against Kaposi sarcoma in transplant patients. *Transplantation.* 2009;88(4):597-598. doi:10.1097/TP.0b013e3181b15d56
33. Mourah S, Porcher R, Battistella M, et al. Paradoxical simultaneous regression and progression of lesions in a phase ii study of everolimus in classic kaposi's sarcoma. *Br J Dermatol.* 2015;173(5):1284-1287. doi:10.1111/bjd.13897
34. Krown SE, Roy D, Lee JY, et al. Rapamycin with antiretroviral therapy in AIDS-associated Kaposi sarcoma: an AIDS Malignancy Consortium study. *J Acquir Immune Defic Syndr 1999.* 2012;59(5):447-454. doi:10.1097/QAI.0b013e31823e7884
35. Trattner A, Hodak E, David M, Sandbank M. The appearance of Kaposi sarcoma during corticosteroid therapy. *Cancer.* 1993;72(5):1779-1783.

409 **Table 1: Patients and Kaposi sarcoma characteristics**

	<b>Characteristics</b>	<b>Overall population N=145</b>
<b>PATIENTS CHARACTERISTICS</b>	Age, years (IQR)	53 (44 to 62)
	Male gender, n (%)	110 (76)
	Region of birth, n (%)	
	Sub-Saharan Africa/Caribbean	76 (56)
	Mediterranean	47 (35)
	Northern Europe	13 (9)
	NA	9
	Transplanted organ, n (%)	
	Kidney	127 (89)
	Heart	3 (2)
<b>KS CHARACTERISTICS</b>	Liver	5 (3)
	Lung	3 (2)
	Other	5 (4)
	NA	2
	Induction therapy, n (%)	
	Yes	102 (81)
	No	24 (19)
	NA	19
	<i>Treatment of induction</i>	
	Steroids	76 (60)
	ATG	51 (40)
	Anti-IL-2 receptor	33 (26)
	OKT3	8 (6)
	Rejection episodes, n (%)	
	No	79 (59)
	Yes	56 (41)
	NA	10
	<i>Treatment of rejection</i>	
	Steroids	47 (70)
	ATG	10 (15)
	OKT3	3 (5)
	Rituximab	1 (2)
	IVIG	3 (11)
<b>KS CHARACTERISTICS</b>	Immunosuppressive drugs at KS diagnosis	
	CS + CNI + PI	109 (76)
	CS + CNI	20 (14)
	CS + PI	8 (6)
	CS + mTOR inh + CNI or PI	4 (3)
	Other	4 (3)
	KS extension, n (%)	
	Cutaneous only	60 (42)
	Mucosal (+/- cutaneous, w/o visceral)	11 (8)
	Visceral (+/- cutaneous/mucosal)	73 (50)
<b>KS CHARACTERISTICS</b>	NA	1
	Lymph node involvement, n (%)	39 (33)
	Gastrointestinal involvement	47 (36%)

	Pulmonary KS, n (%)	29 (20)
	HHV8 detection	
	Positive HHV8 viral load, n (%)	29 (54)
	Positive LANA IHC, n (%)	88 (98)
	Positive latent IF serology, n (%)	74 (91)

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411 ATG, antithymocyte globulin; CNI, calcineurin inhibitor; CS: corticosteroids; IF,  
412 immunofluorescence; IHC, immunohistochemistry; IL-2, interleukine-2; IVIG, intravenous  
413 immunoglobulin; KS, Kaposi sarcoma; mTOR inh: mammalian target of rapamycin inhibitor;  
414 NA, not available; OKT3, anti-CD3 antibody; PI, purine inhibitor.  
415 Other immunosuppressive drugs at KS diagnosis: no treatment (n=1), CNI alone (n=1),  
416 CNI+PI (n=1), unknown treatment (n=1).  
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419 **Table 2: Characteristics of patients in the 4 first-line treatment groups**

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Variable (n, %)	First line treatment of KS				<i>P</i>
	No conversion to mTOR inhibitor		Conversion to mTOR inhibitor		
	Group 1: No chemotherapy	Group 2: With chemotherapy	Group 3: No chemotherapy	Group 4:With chemotherapy	
Mean age (SD), years	52.8 (13.3)	42.2 (17.7)	55.9 (13.7)	47.5 (10.4)	0.010
Male gender	70 (76)	12 (92)	22 (73)	6 (60)	0.34
Sub-Saharan/Caribbean origin	43 (49)	4 (31)	15 (58)	9 (90)	0.030
Median time to KS diagnosis (IQR), months	19 (10 to 40)	14 (8 to 39)	15 (8 to 35)	16 (10 to 24)	0.76
Mucosal KS	14 (15)	2 (15)	6 (20)	2 (20)	0.87
Lymph node involvement	18 (20)	5 (38)	7 (23)	9 (90)	<0.000 1
Symptomatic visceral KS	5 (6)	5 (38)	4 (14)	6 (67)	<0.000 1
HSV prophylaxis	23 (33)	5 (56)	17 (61)	7 (70)	0.021
Overall	92 (63)	13 (9)	30 (21)	10 (7)	-

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423 IQR, interquartile range; KS, Kaposi sarcoma; mTOR, mammalian target of rapamycin

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**Figure legends**

**Figure 1: First-line treatment combination for post-transplant Kaposi sarcoma.**

Strategies included combination of reduction of immunosuppression, conversion mTOR inhibitors and chemotherapy.

**Figure 2: Response at 6 months to first-line treatment.**

Responses classified as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) in the response-evaluable population (n=137) are plotted for each group of treatment.

**Figure 3: Survival analyses for patients with post-transplant Kaposi sarcoma.**

Left, Unadjusted Kaplan-Meier curves for progression-free survival according to first-line treatment; right, Adjusted Kaplan-Meier curves for progression-free survival between patients receiving mTOR inhibitors or not. The group of patients receiving chemotherapy was too small to be included in the adjusted analyses.

Fig 1

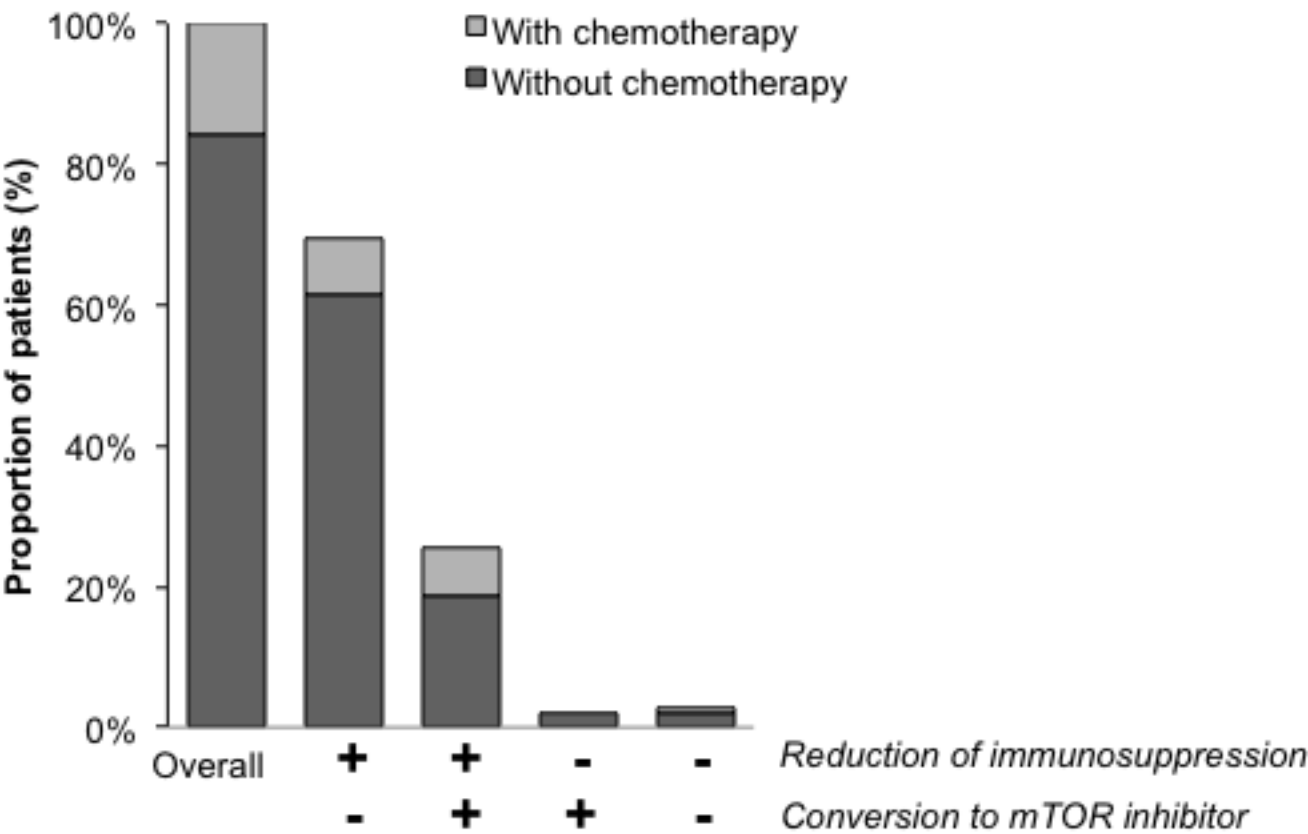




Fig 2

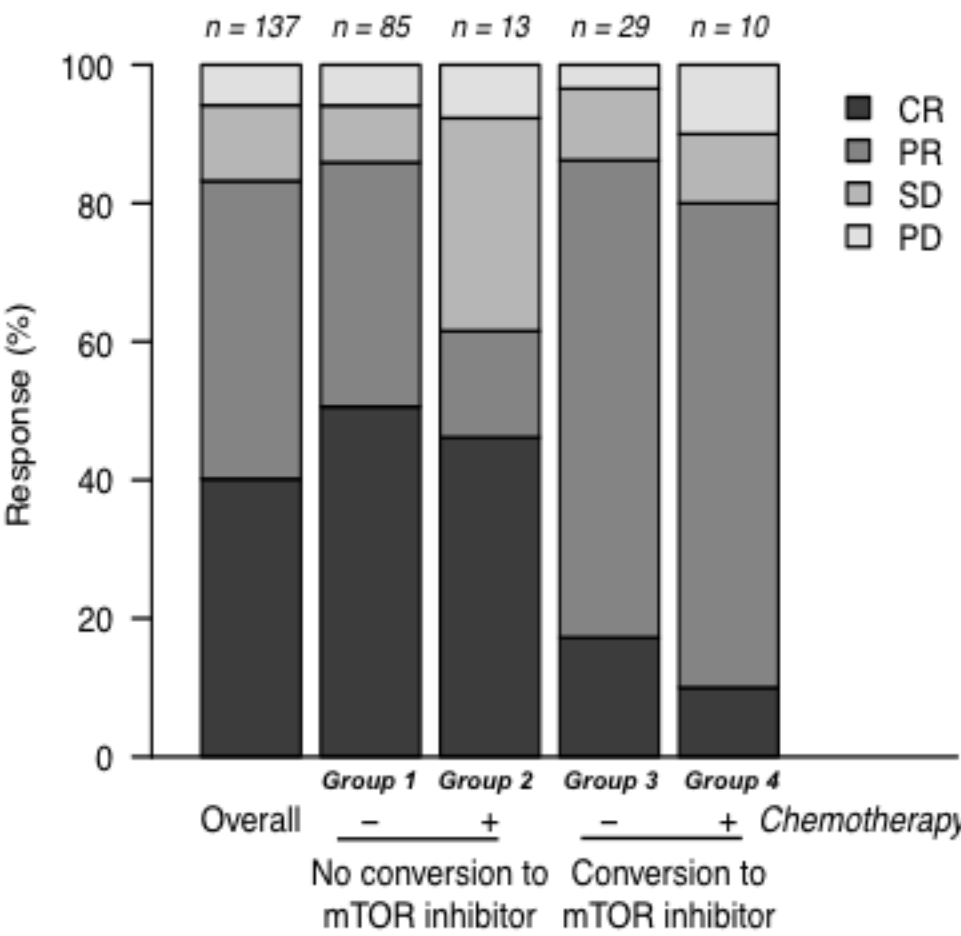


Fig 3

