



**HAL**  
open science

## Management of Kaposi sarcoma after solid organ transplantation: A European retrospective study

Julie Delyon, Clementine Rabate, Sylvie Euvrard, Catherine A. Harwood, Charlotte Proby, A.Tülin Güleç, Deniz Seçkin, Veronique del Marmol, Jan Nico Bouwes-Bavinck, Carla Ferrándiz-Pulido, et al.

### ► To cite this version:

Julie Delyon, Clementine Rabate, Sylvie Euvrard, Catherine A. Harwood, Charlotte Proby, et al.. Management of Kaposi sarcoma after solid organ transplantation: A European retrospective study. *Journal of The American Academy of Dermatology*, 2019, 81, pp.448 - 455. 10.1016/j.jaad.2019.03.028 . hal-03488155

**HAL Id: hal-03488155**

**<https://hal.science/hal-03488155>**

Submitted on 20 Dec 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

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

3  
4 Julie DELYON<sup>1\*</sup> MD PhD, Clementine RABATE<sup>\*2</sup> MD, Sylvie EUVRARD<sup>3</sup> MD,  
5 Catherine A. HARWOOD<sup>4</sup> MD PhD, Charlotte PROBY<sup>5</sup> FRCP, A.Tülin GÜLEÇ<sup>6</sup> MD, Deniz  
6 SEÇKIN<sup>6</sup> MD, Veronique DEL MARMOL<sup>7</sup> MD PhD, Jan Nico BOUWES-BAVINCK<sup>8</sup> MD  
7 PhD, Carla FERRÁNDIZ-PULIDO<sup>9</sup> MD PhD, Maria Andrea OCAMPO<sup>10</sup> MD, Stephane  
8 BARETE<sup>11</sup> MD PhD, Christophe LEGENDRE<sup>2</sup> MD PhD, Camille FRANCÈS<sup>12°</sup> MD PhD,  
9 Raphael PORCHER<sup>13°</sup> MD PhD, Celeste LEBBE<sup>1°</sup> MD PhD, and the Skin Care in Organ  
10 Transplant Patients Europe (SCOPE) group

11 \* co-first authors

12 ° co-last authors

13  
14 **Author affiliations**

15 1 AP-HP Hopital Saint Louis, Department of Dermatology; INSERM U976; Université Paris  
16 Diderot, Sorbonne Paris Cité, Paris, France

17 2 Service de Néphrologie-Transplantation Adultes, Hôpital Necker, AP-HP, Paris and  
18 Université Paris Descartes, Paris, France

19 3 Department of Dermatology, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon,  
20 France

21 4 Centre for Cell Biology and Cutaneous Research, Blizard Institute, Barts and the London  
22 School of Medicine and Dentistry, Queen Mary University of London, London, U.K.

23 5 Dermatology, School of Medicine, University of Dundee, Dundee DD1 9SY, UK.

24 6 Department of Dermatology, Başkent University Faculty of Medicine, Ankara, Turkey

25 7 Dermatology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

- 26 8 Department of Dermatology, Leiden University Medical Center, Leiden, The Netherlands
- 27 9 Department of Dermatology, Hospital Universitari Vall d'Hebron, Barcelona, Spain
- 28 10 Department of Dermatology, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon,
- 29 France (moved to Dermatology Department, Sanitas Foundation, Colsanitas Clinic, Bogotá
- 30 Colombia)
- 31 11 Sorbonne Université, Unit of Dermatology, AP-HP Pitié-Salpêtrière Hospital, Paris,
- 32 France
- 33 12 Sorbonne Université, Service de Dermatologie et Allergologie, AP-HP Hôpital Tenon,
- 34 Paris, France
- 35 13 AP-HP, Centre d'Épidémiologie Clinique, Hôpital Hôtel-Dieu, Paris, France; ; CRESS
- 36 INSERM U1153 ; Université Paris Descartes, Sorbonne Paris Cité.

37

38 **Corresponding author:**

39 Dr Julie DELYON

40 Dermatology Department - AP-HP Hôpital Saint Louis ; 1 avenue Claude Vellefaux – 75475

41 Paris Cedex 10 ; Tel: +33142494679; Fax: +33142499078; Julie.delyon@aphp.fr

42

43 **Funding sources:** none

44 **Disclosure**

45 ATG, C F-P, CH, CP, DS, JD, JNBB, OCa, RP, SB, SE, VDM had no competing interest to

46 declare;

47 CLeg reports personal fees from Astellas, other from Alexion, outside the submitted work;

48 CL received research grants or honoraria from Roche, BMS, MSD, GSK, Novartis, Amgen,

49 outside the submitted work.

50

51 **Word count:**

52 Abstract: 158

53 Text: 2521

54 Material: 2 tables; 3 figures

55 References: 35

56

57

58 **Author contribution**

59 CL and CF conceived and designed the study;

60 CR, CL, CLeg, SE, CH, CP, ATG, DS, VDM, JBB, MAO, CFP, CF, SB (Investigators)

61 participated in data collection and critically reviewed the manuscript;

62 RP constructed the statistical design and performed data analysis;

63 CL, JD, RP participated in writing the paper and contributed to the analysis of study results;

64 CL, JD, RP participated in revision of the article.

65 **ABSTRACT**

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

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

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

73 **Results:** Ninety five percent, 28% and 16% of patients had reduction of immunosuppression,  
74 conversion to mTOR inhibitor and chemotherapy, respectively. Patients treated with  
75 chemotherapy or mTOR inhibitor conversion were more likely to have visceral KS. Overall,  
76 83% of patients had response at 6 months including 40% complete responses (CR).

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

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

81

## 82 INTRODUCTION

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

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

102 Therapy for post-transplant KS has changed over the past two decades. In 2005, conversion to  
103 mTORi was shown to have a therapeutic effect: conversion from calcineurin inhibitors (CNI)  
104 and/or purine antagonists to sirolimus induced responses in 72-100% of patients<sup>13,14</sup>.

105 However, relapse and the apparent absence of remission in patients with visceral KS were  
106 reported in a significant proportion of patients treated with sirolimus<sup>14,15</sup>. Chemotherapy is

107 usually required in patients with visceral involvement or rapidly evolving KS and their use  
108 has been best evaluated in AIDS-related KS<sup>16,17</sup>. The therapeutic armamentarium against post-  
109 transplant KS is now based upon 3 axes –reduction of IS, conversion to mTORi and use of  
110 chemotherapy. However, neither comparative prospective trials nor retrospective studies have  
111 been conducted in post-transplant KS, and no consensus guidelines are available.

112 We conducted a retrospective study amongst expert European centers belonging to the Skin  
113 Care in Organ Transplant Patients, Europe (SCOPE)network, in order to obtain an overview  
114 of the efficacy of treatment and prognosis in post-transplant KS.

115

116

## 117 **MATERIALS AND METHODS**

### 118 **Patients**

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

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

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

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

136

### 137 **Statistical analyses**

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



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

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

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

159

## 160 RESULTS

### 161 Patient characteristics

162 145 patients with post-transplant KS diagnosed between February 1985 and April 2011 were  
163 enrolled (France, n=109; United-Kingdom, n=14; Turkey, n=9; Belgium, n=7; Netherlands,  
164 n=4; Spain, n=2). Ninety-one patients were diagnosed with KS after 2005, when the first  
165 study highlighting the benefits of mTORi in post-transplant KS was reported<sup>13</sup>. Baseline  
166 characteristics are summarized in **Table 1**. Seventy-six percent of patients were male, with a  
167 median age of 53 years. Most patients were kidney transplant recipients (89%).

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

172 Fifty-one percent of patients had visceral KS, which was symptomatic for 20 patients  
173 (14%). Pulmonary KS was reported in 20% of patients.

174

### 175 First-line therapeutic management

176 First-line therapeutic management was highly variable between patients (**Figure 1**).  
177 Nevertheless, most patients shared the common feature of having reduction of IS (95%),  
178 which included dose reduction or drug withdrawal for CNI, MMF, azathioprine or  
179 corticosteroids. Conversion to mTORi was performed in 28% of patients, mostly in  
180 association with reduction of other drugs. Among patients whose KS was diagnosed after  
181 2005 (n=91), 67% had conversion to mTORi, vs. 3% among patients before 2005.

182 Chemotherapy, usually required for severe KS<sup>22,23</sup>, was used as first line for 23  
183 patients (16%), in addition to reduction of IS (n=12, 8%) or conversion to mTORi (n=10,  
184 7%). Cytotoxic agents included liposomal doxorubicin (n=9), bleomycin monotherapy (n=4),

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

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

189

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

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

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

209

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

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

220 The two most used therapeutic options, which were reduction of IS (97% of patients in  
221 Group 1), and reduction of IS associated with conversion to mTORi (90% of patients in  
222 Group 3), had a similar response rate of 86%. Conversion to mTORi induced 17% CR and  
223 69% PR. However, patients who did not receive mTORi achieved more CR ( $P=0.0002$ ) but  
224 not more overall responses (CR+PR) (**Figure 2**).

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

230 Patients with KS relapse or who progressed upon first line treatment (n=52) were  
231 treated with chemotherapy (n=25, 52%), additional reduction of immunosuppression (n=24,  
232 46%) and/or switch to mTORi (15%).

233

## 234 **Survival**

235 The median follow-up time was 91 months from KS diagnosis (7.6 years, range 1 to 276  
236 months). During follow-up, 37 patients died, including 4 deaths due to KS (3%) and 3 of  
237 unknown causes. OS was 82% at 5 years(95%CI:75-89%), and 64% at 10 years(95%CI:54-  
238 75%). OS was not related to KS extent at diagnosis.

239 Differences in PFS were found between the four Groups ( $P=0.0008$ ) (**Figure 3B**), with better  
240 PFS in Group 1 patients. However, treatment groups differed according to patient baseline  
241 characteristics, specifically the extent of disease (**Table 2**). To account for this confounding  
242 due to baseline imbalance in potential prognostic factors, IPTW estimators and regression  
243 adjustment were used to compare PFS between patients receiving mTORi or not (but not  
244 chemotherapy as this group was too small sample size). Results were similar for unadjusted,  
245 IPTW and adjusted analyses, with hazard ratios(HRs) for mTORi vs. no mTORi of  
246 2.18(95%CI:1.18-4.05), 2.22(1.23-4.03) and 2.45(1.29-4.645), respectively (**Figure 3**).

247

#### 248 **Graft survival**

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

## 253 **DISCUSSION**

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

258 mTORi were included in the armamentarium of immunosuppressive drugs since  
259 2000<sup>24</sup>. In 2005, Stallone and colleagues demonstrated that mTOR inhibitors induced CR in  
260 100% of 15 patients with post-transplant KS<sup>13</sup>. This effective strategy based on CNI  
261 withdrawal and switch to mTORi was confirmed in other studies<sup>14,25-27</sup>, although Lebbé et al.  
262 reported a significant proportion of relapses (3/14 patients) and resistance in patients with  
263 visceral KS<sup>14</sup>. Switch to mTORi became part of the standard management strategy of post-  
264 transplant KS<sup>22,23</sup>. In the present study, conversion to mTORi induced responses in more than  
265 80% of patients. However these patients -who certainly had more visceral KS-experienced  
266 fewer CRs than those who did not receive mTORi. Statistical maneuvers to adjust for  
267 important prognostic factors such as disease extent were undertaken. Despite this, the long-  
268 term risk of disease progression remained significantly higher in OTR who received mTORi.

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

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

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

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

299 This study provides insight into clinical practices in post-transplant KS management,  
300 which is based on reduction of IS in addition to conversion to mTORi, and/or chemotherapy.  
301 The signal from our data that mTORi conversion may be associated with a higher risk of  
302 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.

305



306 **REFERENCES**

- 307 1. Schulz TF. Cancer and viral infections in immunocompromised individuals. *Int J*  
308 *Cancer*. 2009;125(8):1755-1763. doi:10.1002/ijc.24741
- 309 2. Francès C, Mouquet C, Marcelin AG, et al. Outcome of kidney transplant recipients with  
310 previous human herpesvirus-8 infection. *Transplantation*. 2000;69(9):1776-1779.
- 311 3. Francès C, Marcelin AG, Legendre C, et al. The impact of preexisting or acquired  
312 Kaposi sarcoma herpesvirus infection in kidney transplant recipients on morbidity and  
313 survival. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*.  
314 2009;9(11):2580-2586. doi:10.1111/j.1600-6143.2009.02816.x
- 315 4. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people  
316 with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-  
317 analysis. *Lancet Lond Engl*. 2007;370(9581):59-67. doi:10.1016/S0140-6736(07)61050-  
318 2
- 319 5. Farge D. Kaposi's sarcoma in organ transplant recipients. The Collaborative  
320 Transplantation Research Group of Ile de France. *Eur J Med*. 1993;2(6):339-343.
- 321 6. Penn I. Kaposi's sarcoma in transplant recipients. *Transplantation*. 1997;64(5):669-673.
- 322 7. Dantal J, Hourmant M, Cantarovich D, et al. Effect of long-term immunosuppression in  
323 kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin  
324 regimens. *Lancet Lond Engl*. 1998;351(9103):623-628. doi:10.1016/S0140-  
325 6736(97)08496-1
- 326 8. Barete S, Calvez V, Mouquet C, et al. Clinical features and contribution of virological  
327 findings to the management of Kaposi sarcoma in organ-allograft recipients. *Arch*  
328 *Dermatol*. 2000;136(12):1452-1458.
- 329 9. Geissler EK, Schlitt HJ, Thomas G. mTOR, cancer and transplantation. *Am J Transplant*  
330 *Off J Am Soc Transplant Am Soc Transpl Surg*. 2008;8(11):2212-2218.  
331 doi:10.1111/j.1600-6143.2008.02391.x
- 332 10. Campistol JM, Eris J, Oberbauer R, et al. Sirolimus therapy after early cyclosporine  
333 withdrawal reduces the risk for cancer in adult renal transplantation. *J Am Soc Nephrol*  
334 *JASN*. 2006;17(2):581-589. doi:10.1681/ASN.2005090993
- 335 11. Euvrard S, Morelon E, Rostaing L, et al. Sirolimus and secondary skin-cancer  
336 prevention in kidney transplantation. *N Engl J Med*. 2012;367(4):329-339.  
337 doi:10.1056/NEJMoa1204166
- 338 12. Hoogendijk-van den Akker JM, Harden PN, Hoitsma AJ, et al. Two-year randomized  
339 controlled prospective trial converting treatment of stable renal transplant recipients with  
340 cutaneous invasive squamous cell carcinomas to sirolimus. *J Clin Oncol*.  
341 2013;31(10):1317-1323. doi:10.1200/JCO.2012.45.6376
- 342 13. Stallone G, Schena A, Infante B, et al. Sirolimus for Kaposi's sarcoma in renal-  
343 transplant recipients. *N Engl J Med*. 2005;352(13):1317-1323.  
344 doi:10.1056/NEJMoa042831

- 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

- 382 27. Gutiérrez-Dalmau A, Sánchez-Fructuoso A, Sanz-Guajardo A, et al. Efficacy of  
383 conversion to sirolimus in posttransplantation Kaposi's sarcoma. *Transplant Proc.*  
384 2005;37(9):3836-3838. doi:10.1016/j.transproceed.2005.10.076
- 385 28. Hojo M, Morimoto T, Maluccio M, et al. Cyclosporine induces cancer progression by a  
386 cell-autonomous mechanism. *Nature.* 1999;397(6719):530-534. doi:10.1038/17401
- 387 29. Guba M, Graeb C, Jauch K-W, Geissler EK. Pro- and anti-cancer effects of  
388 immunosuppressive agents used in organ transplantation. *Transplantation.*  
389 2004;77(12):1777-1782.
- 390 30. Datta D, Contreras AG, Basu A, et al. Calcineurin inhibitors activate the proto-oncogene  
391 Ras and promote protumorigenic signals in renal cancer cells. *Cancer Res.*  
392 2009;69(23):8902-8909. doi:10.1158/0008-5472.CAN-09-1404
- 393 31. Roy D, Sin S-H, Lucas A, et al. mTOR inhibitors block Kaposi sarcoma growth by  
394 inhibiting essential autocrine growth factors and tumor angiogenesis. *Cancer Res.*  
395 2013;73(7):2235-2246. doi:10.1158/0008-5472.CAN-12-1851
- 396 32. Barozzi P, Riva G, Vallerini D, et al. Indirect antitumor effects of mammalian target of  
397 rapamycin inhibitors against Kaposi sarcoma in transplant patients. *Transplantation.*  
398 2009;88(4):597-598. doi:10.1097/TP.0b013e3181b15d56
- 399 33. Mourah S, Porcher R, Battistella M, et al. Paradoxical simultaneous regression and  
400 progression of lesions in a phase ii study of everolimus in classic kaposi's sarcoma. *Br J*  
401 *Dermatol.* 2015;173(5):1284-1287. doi:10.1111/bjd.13897
- 402 34. Krown SE, Roy D, Lee JY, et al. Rapamycin with antiretroviral therapy in AIDS-  
403 associated Kaposi sarcoma: an AIDS Malignancy Consortium study. *J Acquir Immune*  
404 *Defic Syndr 1999.* 2012;59(5):447-454. doi:10.1097/QAI.0b013e31823e7884
- 405 35. Trattner A, Hodak E, David M, Sandbank M. The appearance of Kaposi sarcoma during  
406 corticosteroid therapy. *Cancer.* 1993;72(5):1779-1783.

407

408

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)
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)	
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)

410

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).

417

418

419 **Table 2: Characteristics of patients in the 4 first-line treatment groups**

420

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
<b>Overall</b>	<b>92 (63)</b>	<b>13 (9)</b>	<b>30 (21)</b>	<b>10 (7)</b>	-

421

422

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

424

425

426

427

428 **Figure legends**

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

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

432

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

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

437

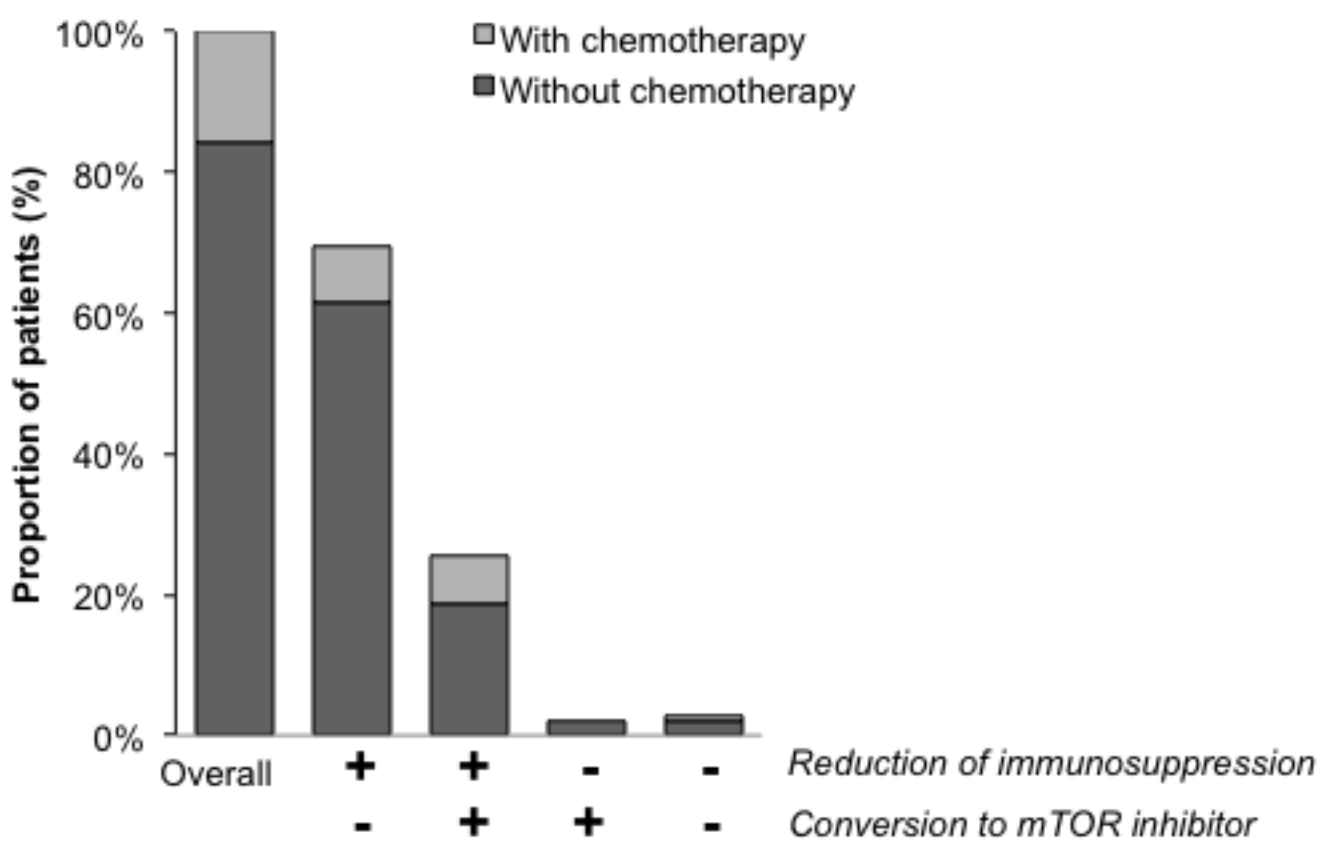
438 **Figure 3: Survival analyses for patients with post-transplant Kaposi sarcoma.**

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

443

444

Fig 1





**Fig 2**

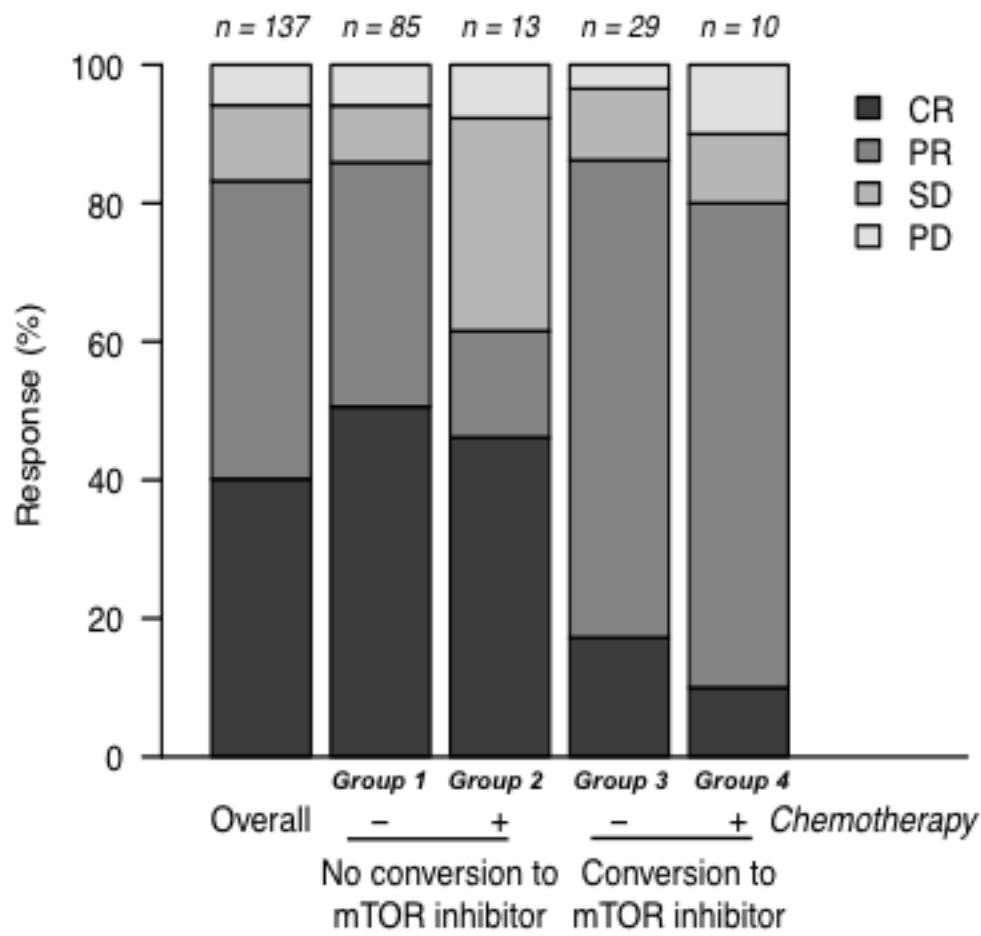


Fig 3

