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## Original Research

# Diagnosis and treatment of Kaposi's sarcoma: European consensus-based interdisciplinary guideline (EDF/EADO/EORTC)



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**Abstract** Kaposi's sarcoma (KS) is a multifocal neoplasm of lymphatic endothelium-derived cells infected with human herpesvirus 8. Four clinical subtypes are distinguished: the classic, the endemic, the epidemic subtype in HIV positive patients and the iatrogenic subtype. The diagnosis is primarily based on clinical features and confirmation by histology with immunohistochemistry. Cutaneous distribution and severity, mucosal, nodal and visceral involvement depend on the type of KS with in general indolent behaviour and chronic evolution in the classic subtype and the more severe forms in iatrogenic or epidemic subtypes. Management should aim at achieving disease control. For localised lesions, several local therapies have been developed without randomised trial comparisons. Radiotherapy, intralesional chemotherapies and electrochemotherapy have high response rates. Topical treatments—imiquimod or topical 9-cis-retinoid acid—can also be used. Systemic treatments are reserved for locally aggressive extensive and disseminated KS: the recommended first-line agents are pegylated liposomal doxorubicin (PLD) and paclitaxel. In CKS, PLD or low-dose interferon-alfa are the recommended first-line agents in younger patients. In AIDS-related KS, combination antiretroviral therapy is the first treatment option; specific systemic treatment is needed only in case of extensive disease and in the prevention and treatment of immune reconstitution inflammatory syndrome. In post-transplant KS, tapering down immunosuppressive therapy and switching to mammalian target of rapamycin (m-TOR) inhibitors are used. Follow-up schedules for patients with KS disease depend on aggressiveness of the disease.

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## 1. Introduction

These guidelines have been written under the auspices of the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization for Research and Treatment of Cancer (EORTC) to help clinicians treating patients suffering from Kaposi's sarcoma (KS) in Europe, especially in countries where national guidelines are lacking.

It is our hope that these guidelines will assist health-care providers in defining local policies and standards of care and will foster progress towards an European consensus on the management of KS. It is not intended to replace national guidelines but to serve as basis for the development of these. The guidelines deal with all clinical settings of KS. The guidelines are also intended to promote the integration of care between medical and paramedical specialities for the benefit of patients.

These guidelines reflect the best published data available at the time the report was prepared. Caution

should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to deviate from these guidelines in the interest of specific patients or under special circumstances. Just as adherence to the guidelines may not constitute defence against a claim of negligence, deviation from them should not necessarily be deemed negligent.

## 2. Methods

To construct this EDF-EADO-EORTC guideline, a PubMed search with the terms 'Kaposi's sarcoma' and 'Kaposi' without any language restriction was conducted, and the results were submitted to the writing panel. We excluded case reports. We also searched for the latest versions of existing guidelines and for systematic reviews using PubMed (<http://www.ncbi.nlm>

nih.gov/pubmed), Google (<https://www.google.com>) and Embase (<https://www.embase.com>).

In preparation of the manuscript, the panel looked for differences between retrieved guidelines. The manuscript was circulated and commented by the expert panel with members from EADO, EDF and EORTC in several rounds, before producing the final version.

The present guidelines contain recommendations according to Oxford level of evidence 2011 and grade of recommendation with A: strong recommendation/shall; B: recommendation/should; 0: recommendation pending/may, can.

### 3. Definition

KS is a multicentric neoplasm of lymphatic endothelium-derived cells infected with Kaposi's sarcoma-associated herpesvirus (KSHV) otherwise called human herpesvirus-8 (HHV-8) [1,2].

Four recognised clinical subtypes can be distinguished: the sporadic or classic subtype initially described by Kaposi, the endemic subtype observed in sub-Saharan Africans, the epidemic subtype in patients infected with the human immunodeficiency virus (HIV) and the iatrogenic subtype observed in patients treated with immunosuppressive therapy, especially organ transplant recipients. Whatever the clinical subset, KS occurs in patients infected by HHV-8, and the level of immunosuppression is the main factor for the development and progression of the disease [1,2].

### 4. Epidemiology

#### 4.1. Classic or mediterranean KS

##### 4.1.1. Incidence

Classic KS (CKS) incidence is higher in Mediterranean countries compared with Northern countries. It was estimated to be 0.014 cases per 100,000 person years in the UK between 1971 and 1980 and up to a standardised incidence of 1.58/100,000 inhabitants per year in Sardinia between 1977 and 1991 [3].

CKS predominates in men with a sex ratio of 2:1 and 5:1 in Italy and Israel, respectively. For unknown reasons, sex ratio currently tends to decrease [3–5]. Incidence exponentially increases with age [3–5]. In Israel, the median age of diagnosis is 69.5 and 73.5 years, respectively, in men and women [6].

##### 4.1.2. Risk factors

Previous infection by HHV8 is mandatory to develop KS. Therefore, patients originating from countries with medium or high HHV8 seroprevalence such as Mediterranean countries are at higher risk. The same is true for men who have sex with men due to high HHV8 transmission [7]. Age is also an important risk factor [8].

Possible other risk factors for CKS are contact to siliceous volcanic soil and exposition to bloodsucking insects [9,10].

Patients with classical KS have no overall increased risk for secondary malignancies [11].

#### 4.1.3. Mortality

Owing to its slow progression and indolent biologic behaviour, CKS does not seem to impact the mortality rate. A study on 204 CKS from Italian population-based cancer registries showed 5 and 10 year survival rates of 69% and 46%, respectively, with a median survival of 9.4 years, similar to the Italian general population of the same sex and age [12].

#### 4.2. Epidemic KS

##### 4.2.1. Incidence

The incidence of epidemic KS has decreased worldwide since 1995 due to the institution of combination antiretroviral therapy (cART) with a standardised incidence ratio that declined from approximately 4.6 to 0.3 between the early 1990s to late 1990s [13–17]. In Africa, the incidence has also been considerably reduced with cART [18–20]. However, KS is still the second common cancer in HIV-infected patients in Western countries and remains a public health problem in sub-Saharan Africa [21,22].

##### 4.2.2. Risk factors

With widespread use of effective cART, the risk of KS has declined dramatically in the HIV population. A low CD4 cell count remains the main risk factor in HIV-infected cART-treated homosexual men, in Western countries [23]. However, the risk of HIV-associated KS remains elevated as compared with the risk in the general population even among patients who have normal CD4<sup>+</sup> counts and/or undetectable HIV RNA [24]. In Africa, risk factors for HIV-related KS are not receiving cART, male gender, low CD4 count and, to a lesser extent, age [18,20].

##### 4.2.3. Mortality

Mortality of epidemic KS has also dramatically decreased. In Western countries, the cumulative survival at 24 months ranges from 71% for patients with a CD4 cell count of less than 300/mm<sup>3</sup> at KS diagnosis to 94% for those with a CD4 cell count of more than 300/mm<sup>3</sup> [23].

##### 4.2.4. Post-transplant KS

KS prevalence after organ transplantation parallels the overall prevalence of HHV-8 infection in the different countries: high (>50%) HHV-8 prevalence in sub-Saharan Africa, intermediate HHV-8 seroprevalence (10%–20%) in Mediterranean countries as well as in South America and West Africa and very low

prevalence areas in Northern Europe and the United States (less than 5%) [25].

#### 4.2.5. Risk factors

The risk of KS in organ transplant recipients is 50- to 500-fold higher compared with the general population. It increases with the recipient's age at transplantation, the number of mismatches at the HLA-B locus and a more aggressive immunosuppressive regimen. The male-to-female ratio ranges from 2 to 40. KS risk peaks in the first 2 years after transplantation and decreases thereafter. The median time between organ transplantation and KS onset is 13 months, with a range of a few weeks to 18 years. Most cases of post-transplant KS develop as a result of HHV-8 reactivation [25–29].

#### 4.2.6. Mortality

The mortality rate linked to KS is currently lower than previously reported in the literature. In a recent French series, renal graft survival in post-kidney transplant KS was 85% and 75% at 5 and 10 years, respectively, similar to overall survival in kidney transplant recipients [30].

### 5. Clinical presentation

KS typically presents with purplish, reddish blue or dark/brown macules, plaques and/or nodules that may bleed, ulcerate, become verrucous and hyperkeratotic [2,31]. Lymphoedema is frequent and can precede maculopapular lesions [2,31]. Dermoscopy may be helpful in raising the suspicion for KS especially for solitary nodules by displaying the classical colours (purple, yellow-green, blue and red) of vascular tumours [32]. Cutaneous distribution and severity and mucosal, nodal and visceral involvement, for example, lung, gastrointestinal, bone and liver involvement, depend on the type of KS as summarised in Table 1. CKS has as a rule an indolent behaviour, whereas epidemic and post-transplant KS may be extensive and life threatening.

### 6. Histological diagnosis

Biopsy is mandatory for diagnosis. Histology is essentially identical in the different epidemiologic types of KS [33]. Patch stage typically arises in the reticular dermis and is marked by proliferation of small, irregular and jagged endothelial-lined spaces surrounding normal

dermal vessels and adnexal structures accompanied by a variable, inflammatory lymphocytic and plasma cell infiltrate. Plaque-stage KS lesions are characterised by the proliferation of spindle-cells throughout the whole dermis and sometimes the subcutis. Spindle cells are dispersed throughout dermal collagen bundles forming irregular, cleft-like vascular channels containing erythrocytes. Neoangiogenesis is also present. KS lesions also contain several hemosiderin-loaded macrophages. Nodular-stage KS lesions are characterised by fascicles of spindle cells with mild to moderate cytologic atypia, often mixed with a variable chronic inflammatory infiltrate composed of lymphocytes, plasma cells and dendritic cells and a network of slit-like vascular spaces. This pathological classification carries no prognostic value [33]. Exceptional anaplastic cases with highly atypical cells and poor differentiation have been reported with poor prognosis [34].

KS cells stain for endothelial cell markers such as CD34 and CD31. Most spindle cells also have lymphatic endothelial cell features as shown by expression of D2-40 (which binds to the podoplanin antigen), LYVE-1 (homologue of the CD44 glycoprotein receptor for hyaluronan), VEGFR-3 (the receptor for vascular endothelial growth factor C) and Prox-1 [35]. The identification and localisation of HHV8 within KS lesional cells using a monoclonal antibody against HHV-8 latent nuclear antigen (LANA) is the most diagnostically helpful immunostaining technique available to differentiate KS from its simulators because it is specific of KS [35,36].

### 7. HHV-8 diagnostic tools

Apart from immunohistochemistry using a monoclonal antibody against LANA on paraffin-embedded sections, no other specific HHV-8 tool is routinely used. Serologic tests and HHV-8 DNA sequences detection using polymerase chain reaction (PCR) are available on an individual basis [31].

#### 7.1. Serology

Various tests have been developed based on immunofluorescence, Western blot and enzyme-linked immunosorbent assays to detect antibodies against latent and lytic genes. So far, effective tools are available for

Table 1  
Clinical features of KS.

| Type of KS                | Cutaneous involvement                 | Mucosal involvement | Visceral involvement | Lymph node involvement |
|---------------------------|---------------------------------------|---------------------|----------------------|------------------------|
| <b>Classic/endemic KS</b> | Indolent, predominance on extremities | ≤5% [86,87]         | <10% [88]            | <10% [88]              |
| <b>AIDS-associated KS</b> | More widespread and extensive [89]    | 30–40% [90]         | 20–40% [89,90]       | 25% [89,90]            |
| <b>Post-transplant KS</b> | More widespread and extensive [30,91] | 20%<br>[30,91]      | 20–50%<br>[30,91]    | 20–40% [91,30]         |

KS, Kaposi's sarcoma.

Table 2  
Prognostic factors of KS.

| Type of KS                                               | Prognostic factors                                                                                                                                                                                                                |
|----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Classic/endemic KS</b> [86]<br>Level of evidence 3    | - Immunosuppression<br>- Older age                                                                                                                                                                                                |
| <b>AIDS-associated KS</b> [89,92]<br>Level of evidence 2 | - Age $\geq$ 50 years<br>- Occurrence of KS at or after AIDS onset<br>- Immune status (CD4 counts)<br>- Detectable HHV-8 viraemia<br>- Presence of systemic symptoms<br>- Having another AIDS-associated illness at the same time |
| <b>Post-transplant KS</b><br>Level of evidence 3         | Not formally investigated. Prognosis relies on the feasibility of minimizing immunosuppression and not on KS extension                                                                                                            |

KS, Kaposi's sarcoma; HHV-8, human herpesvirus-8.

seroepidemiological studies, but their usefulness in clinical daily practice is debated [31].

### 7.2. Polymerase chain reaction

PCR-based methods may be successfully used to detect HHV-8 viral sequences in various specimens, for instance, in KS lesions, with a very high specificity and sensitivity. HHV-8 sequences can also be detected in the plasma and in peripheral blood mononuclear cells. Although HHV-8 viral load in peripheral blood mononuclear cells of KS individuals correlates with tumour burden, this test cannot be used in clinical practice to monitor KS patients or to predict the occurrence of KS in transplant recipients due to low interval variations [31].

## 8. Pathogenesis

KS spindle cells are infected by HHV-8 and considered to be of endothelial origin [37].

A number of HHV8 gene products are able to activate signalling pathways involved in angiogenesis and vascular differentiation [38,39]. KS tumours have been shown to be polyclonal or oligoclonal or monoclonal [40–42]. Some cases of KS are probably true reactive inflammatory lesions. Later on, cellular genetic alterations occurring from KSHV-induced genetic instability could lead to monoclonal proliferations that represent a true malignancy [40–42].

## 9. Prognosis, staging classification and workup

Prognostic factors identified in the CKS, AIDS-associated KS and post-transplant KS are summarised in Table 2.

### 9.1. Staging classification and workup

The only validated staging classification is for AIDS-associated KS. The AIDS Clinical Trials Group Oncology Committee has elaborated a staging system in the pre-cART era, which includes measurement of the disease extent as localised or disseminated (T), severity of immunodeficiency by the CD4 cell number as high or low (I) and the presence of systemic symptoms (S) (Table 3) [43]. In the era of cART, the T and S stages only and not I might be useful to identify patients with poor prognosis [44].

There is no universally accepted staging classification for CKS, endemic KS and post-transplant KS. Patient management should distinguish 3 situations: **localised non-aggressive, locally aggressive and disseminated KS**.

For CKS, endemic KS and post-transplant KS evaluation and staging, workup should be discussed on an individual basis depending on the symptoms and the rate of lesion development. A staging workup according to the 3 subtypes of KS disease is proposed from our experience in Table 4 [45,46].

Table 3  
AIDS-related KS.

| Factor               | Good prognosis (0)                                                                                                                                                                                                                              | Poor prognosis (1)                                                                                                                                       |
|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
|                      | (Any of the following)                                                                                                                                                                                                                          | (Any of the following)                                                                                                                                   |
| Tumour (T)           | Confined to skin and/or lymph nodes and/or minimal oral disease [Note: Minimal oral disease is non-nodular KS confined to the palate.]                                                                                                          | Tumour-associated oedema or ulceration<br>Extensive oral KS<br>Gastrointestinal KS<br>KS in other non-nodal viscera                                      |
| Immune system (I)    | CD4 cells $\geq$ 150/ $\mu$ L                                                                                                                                                                                                                   | CD4 cells <150/ $\mu$ L                                                                                                                                  |
| Systemic illness (S) | No history of opportunistic infections (OIs) or thrush<br>No 'B' symptoms [Note: 'B' symptoms are unexplained fever, night sweats, >10% involuntary weight loss, or diarrhoea persisting >2 weeks.]<br>Performance status $\geq$ 70 (Karnofsky) | History of OIs and/or thrush<br>'B' symptoms present<br><br>Performance status <70<br>Other HIV-related illness (e.g., neurological disease or lymphoma) |

KS, Kaposi's sarcoma; HIV, human immunodeficiency virus.  
AIDS Clinical Trials Group staging classification [43]

Table 4  
Proposed staging workup (good clinical practice).

| Items                | Classic/endemic KS | AIDS-associated KS | Iatrogenic KS |
|----------------------|--------------------|--------------------|---------------|
| Clinical examination | ++                 | ++                 | ++            |
| HIV serology         | ++                 | ++                 | ++            |
| Standard blood test  | ++                 | ++                 | ++            |
| HHV-8 viremia        | –                  | +                  | +             |
| CD4 count            | –                  | ++                 | +             |
| Histology            | ++                 | ++                 | ++            |
| Total body CT scan   | ±                  | +                  | +             |
| Bronchoscopy         | ±                  | ±                  | ±             |
| GI endoscopy         | ±                  | ±                  | ±             |

CT, computerised tomography; KS, Kaposi's sarcoma; HIV, human immunodeficiency virus; US, ultrasound; GI, endoscopy; HHV-8, human herpesvirus-8.

–: usually not.

+: usually yes.

++: mandatory.

±: according to symptoms.

It practically does not take into account data essential for therapeutic decision such as functional disability, rate of development of KS lesions and KS-linked vital risk, which have to be evaluated on a case-by-case basis.

## 10. Treatment

### 10.1. Local therapies

Localised, symptomatic lesions can be treated using local approaches which are described in the following text. There is no randomised clinical trial comparing these different local treatment modalities. Few controlled studies have been carried out in this area, and it is not possible to compare studies, because of the lack of standardised classification systems for disease activity and clinical outcomes. The main studies are summarised in [Supplementary Table 1](#).

### 10.2. Physical agents

#### 10.2.1. Radiotherapy

Radiotherapy is one of the most efficient treatments for all forms of localised KS. Overall response rates range from 47% to 99% [47–54]. Prescribed radiotherapy doses are 30–36 Gy in 2- or 3-Gy daily fractions using low-energy photons and/or electrons. Higher dose per fractions (>3 Gy per fraction) and concomitant administration of systemic therapies should be avoided to reduce the risk of long-term sequelae. Patients should be informed about the possible risks of out-of-field recurrence and of radiotherapy-induced skin toxicity (telangiectasia, hyperpigmentation, skin atrophy and fibrosis).

#### 10.2.2. Surgical excision

Surgical excision is grievous with a high recurrence rate. It should not be used in extensive lesions but can be applied on a few well-defined limited and superficial

lesions; however, repeated surgical excisions can cause severe functional impairment [55].

### 10.2.3. Cryosurgery and laser

CO<sub>2</sub>-laser and superficial cryotherapy can be temporarily efficient in superficial lesions with 80–90% overall response rate. The patient should be informed on the risk of sequelar hypopigmentation [55,56].

### 10.3. Local or intralesional chemical or immune-modifying agents

Intralesional chemotherapies are a historical approach and have been tested with good response rates (RRs), for example, vinblastine (the most widely used intralesional chemotherapy) with a reported RR of about 70% [57].

Intralesional vincristine was also used for CKS in a prospective trial enrolling 151 patients; at week 12, the response rate was 98.7% [58].

Electrochemotherapy is an interesting new procedure which combines intralesional chemotherapy, usually bleomycin, and electroporation, enhancing drug uptake into tumoural cells. In several prospective trials, electroporation associated with intravenous bleomycin (15,000 IU/m<sup>2</sup>) infusion showed complete response in about 65–89% of cases after 1–3 sessions [59–61].

Imiquimod has been assessed in a prospective, single-center open-label phase II trial for skin lesions of classic or endemic KS and showed antitumour activity in about half of the 17 patients with local itching and erythema reported for 53% of patients [62].

Topical 9-cis-retinoid acid (alitretinoin gel 0.1%) in association with highly active antiretroviral therapy showed 37% partial or total response rate in HIV-related KS [63].

### 10.4. Systemic treatment

Treatment of KS depends on the KS type, the extent of the disease, the disease course and on patient's symptoms. The goal of systemic therapy is not to cure but to achieve disease control and symptom relief with quality of life preservation.

Most data reviewed rely on prospective trials performed before cART on HIV-related KS. Since the cART era, it has become difficult to assess the benefit of a specific agent outside the setting of a controlled trial. For HIV-associated KS, the main studies are summarised in [Supplementary Table 2](#). In CKS, prospective trials are rare and experience relies mostly on retrospective data. Very few data are available on the benefit and tolerance of KS-specific treatment in post-transplant KS.

In terms of systemic treatment, the recommended first-line agents are pegylated liposomal doxorubicin (PLD) and paclitaxel (PCT).

#### 10.4.1. Pegylated liposomal doxorubicin

Administration of 20 mg/m<sup>2</sup> of PLD every 3 weeks allows a best overall response rate of 76% in HIV-related KS in association with cART and 71%–100% in CKS. The median duration of response is around 5 months in HIV-related KS and 25 months in CKS [64]. The safety profile is good with around 5% grade IV neutropenia and 5% hand–feet syndrome [64–67]. For HIV-related aggressive KS and for prevention and treatment of immune reconstitution inflammatory syndrome (IRIS), cART alone is often inadequate, and for such patients, systemic chemotherapy is recommended. PLD is approved as first-line therapy of HIV-related KS.

#### 10.4.2. Paclitaxel

PCT was tested in association with cART in HIV-related KS. PCT given intravenously 100 mg/m<sup>2</sup> every 2 weeks provides a response rate around 60% with reported median response duration of 8.9 months (range: 6.8–11.2 months) [68]. PCT (100 mg/m<sup>2</sup> every 2 weeks) was compared with PLD (20 mg/m<sup>2</sup> every 3 weeks) in a randomised trial and showed comparable median progression-free survival (17.5 versus 12.2 months,  $p = 0.66$ ) with more grade III–V toxicity for PCT, particularly more grade IV neutropenia and mild-to-moderate alopecia [69]. PCT is approved as second line for HIV-related KS [69–71].

PCT was also tested in non–AIDS-related KS with different schedules (low dose: 100 mg weekly for 12 weeks; 175 mg/m<sup>2</sup> every 3 weeks) with major clinical responses of around 80% [70,71]. In general, 80 mg/m<sup>2</sup> weekly in a continuous basis or 3 weeks on 1 week off is the preferred schedule.

Other chemotherapies can sometimes be considered as alternatives but are not used/recommended as first-line therapies. They include vinblastine (3 mg/m<sup>2</sup> IV weekly) [72], etoposide per os (100 mg/day 1–3 up to d 1–5 every 3 weeks) [73,74] and bleomycine (5 mg/day for 3 days every 2 weeks) (level of evidence: 3; grade of recommendation: 0) [75].

#### 10.4.3. Interferon alfa-2a or 2b

Interferon alfa (3 million units 5 times a week for 2 weeks then 2–6 million units 3–6 times a week) was evaluated in CKS with a very good rate of partial response in 71–100% of patients sometimes of long duration [76] (Level of evidence: 4; grade of recommendation: 0).

Interferon alfa was approved for the treatment of AIDS-related KS many years before the availability of cART and liposomal anthracycline. It led to an approval at a very high and poorly tolerated dosage of 20 millions/m<sup>2</sup> which is no longer used. The benefit was dependent on the CD4 levels and mostly seen in cutaneous disease. Limited data are available on the use of low-dose interferon alfa with cART [77].

#### 10.4.4. Antiangiogenic agents (pomalidomide/lenalidomide/bevacizumab)

Pomalidomide and lenalidomide have shown activity in both AIDS-related and CKS, although the number of patients was limited. Pomalidomide was tested in a phase I/II study in 15 HIV-infected patients and 7 HIV-uninfected patients with an overall response rate (ORR) of 60% (95% confidence interval [CI], 32%–84%) and 100% (95% CI, 59%–100%), respectively; median progression-free survival was 16.6 months [78].

Other antiangiogenic drugs such as bevacizumab showed a 31% ORR (95% CI, 11%–58.7%) in a 17-patient phase II trial and deserves further evaluation [79,80].

### 11. Special indications per type of KS

Treatment of KS depends on the setting, the extent, the course and KS subtype. The goal of specific therapy is not to cure but to achieve disease control and symptom relief with quality of life preservation.

#### 11.1. HIV-related KS

cART is the first treatment option in this KS subtype. Currently available antiretroviral drugs belong to 6 classes: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs); non-nucleoside reverse transcriptase inhibitors; protease inhibitors; integrase inhibitors; fusion inhibitors; CCR5 antagonists (anti-CCR5). In 2018, first-line triple therapy remains an association of 2 NRTIs with a third agent. There are many validated options in terms of immunovirological efficacy (<https://cns.sante.fr/actualites/prise-en-charge-du-vih-recommandations-du-groupe-dexperts/>). The choice of the first treatment must be individualised with the patient who must be able to participate in this choice, the objective being to reach a maximum level of compliance. Indeed, the development of cART has resulted in decreased risk of KS in HIV-infected patients and has also been shown to prolong survival in patients who have been treated for KS with chemotherapy. In most cases, HIV-related KS regresses with cART, but systemic chemotherapy is recommended for patients with T1 patients or rapidly progressive disease and in the prevention and treatment of IRIS [80].

Liposomal anthracyclines (first line) and taxanes (second line) have become the established systemic therapy against KS in combination with cART [22]. However, KSHV cannot be eradicated; tumours may recur and patients often require additional therapies. Chronic administration of cytotoxic agents is poorly tolerated, and in this setting, drugs such as pomalidomide/lenalidomide may be discussed.

### 11.2. Post-transplant KS

In the management of post-transplant KS, tapering down immunosuppressive therapy to the lowest possible level and switching to mammalian target of rapamycin (m-TOR) inhibitors such as sirolimus are essential while attempting to keep the allograft functional [81,82,25,83]. Although poorly evaluated in post-transplant KS, specific treatments can be useful in patients with extensive or life-threatening lesions in combination with immunosuppressors minimisation.

In combination with decreasing immunosuppression, patients with extensive or life-threatening post-transplant KS can require the use of systemic treatment, although this is poorly evaluated in this particular KS subtype. Noteworthy, interferon alfa is generally not recommended after organ transplantation because its use is associated with higher rejection risk.

### 11.3. Classic and endemic KS

Aggressive forms characterised by lymph node and/or visceral involvement, severe oedema, local complications or rapid extension require systemic treatment which is poorly codified [84]. The first options are generally based on the use of liposomal anthracyclines and, less frequently, weekly taxanes. Low dose interferon alpha can also be considered as first-line therapy for younger, healthy patients (<70 years old and normal cardiac function) but is often poorly tolerated in elderly patients [85].

## 12. Follow up

Follow-up modalities depend on the KS subtype, the extent and treatment required. Clinical examination, standard blood tests including complete blood count and protein electrophoresis, and potentially radiological

examinations (total body CT scan) should be proposed at variable interval; a follow-up proposal as per the subtypes of KS disease is shown in Table 5 (recommendations based on clinical practice).

In life-threatening conditions (ie, extensive HIV-related KS, IRIS, severe forms of post-transplant KS), clinical evaluation and follow-up will be carried out frequently at least on a monthly basis and radiological evaluation at least every 3 months until disease stabilisation; conversely for CKS which usually has an indolent behaviour, follow-up can be considered every 6–12 months, essentially based on clinical examination. Notably repeated biopsies followed by histological examination are not required but may be useful in case of atypical presentation/evolution or to confirm nodal/visceral involvement.

### Conflict of interest statement

Pr. Dummer has a consulting or advisory role for Amgen, BMS, MSD, Roche, Novartis, Pierre-Fabre, Sanofi, Takeda and Sun Pharma. Pr. Peris has nothing to disclose. Pr. Hoeller has consulting and speaker role for Amgen, BMS, MSD, Novartis, Pierre-Fabre and Roche. Pr. Zalaudek has nothing to disclose. Pr. Spano has consulting role for Roche and MSD; is in the board of Pfizer, Lilly, Astra Zeneca, Leo Pharma and Teva; participates in a symposium of Pfizer, BMS, Pierre-Fabre Oncology, Astra Zeneca, Leo Pharma, Janssen and Novartis and received a grant from MSD Avenir. Pr. Stratigos has consulting role and participates in satellite symposia from BMS, MSD, Roche, Novartis, Pierre-Fabre, Sanofi, Pfizer and Regeneron and received a grant from BMS, Roche, Novartis and Pfizer. Pr. Battistella has consulting role from BMS, Innate Pharma, Leo Pharma, Takeda and Roche and received a research grant from Takeda. Pr. Forsea received personal fees from Novartis and Amgen and non-financial support from Leo Pharma and Amgen. Pr. Bylaite-Bucinskiene has nothing to disclose. Pr. Harwood received honoraria from Sanofi and Novartis; participated in commercial clinical trial from Pellepharm and Novartis; received grant from Novartis and received supply of medication for an investigator-led clinical trial from MEDA. Pr. Vieira has nothing to disclose. Pr. Garbe participates in advisory board of Amgen, BMS, MSD, Novartis, Philogen, Roche and Sanofi and received grant from BMS, Novartis and Roche. Pr. Eggermont participates in advisory board of Actelion, Agenus, Bayer, BMS, Frobion, HalioDX, Incyte, ISAPharmaceuticals, MedImmune, Merck GmbH, MSD, Nektar, Novartis, Polynoma, Regeneron, Roche, Sellas, Sanofi and TheraNovir and participates in DMC from CellDex, Pfizer and Novartis. Pr. Kandolf Sekulovic received speakers's fees, travel expenses from MSD, Roche, Novartis, BMS and Pfizer and non-financial

Table 5

Proposed follow-up (recommendation based on clinical practice).

| Items                | Classic/endemic KS | AIDS-associated KS | Iatrogenic KS |
|----------------------|--------------------|--------------------|---------------|
| Clinical examination | ++                 | ++                 | ++            |
| HIV serology         | –                  | –                  | –             |
| Standard blood test  | +                  | ++                 | ++            |
| HHV 8 viremia        | –                  | –                  | –             |
| CD4 count            | –                  | ++                 | +             |
| Histology            | –                  | –                  | –             |
| Total body CT scan   | ±                  | ±                  | ±             |
| Bronchoscopy         | ±                  | ±                  | ±             |
| GI endoscopy         | ±                  | ±                  | ±             |

CT, computerised tomography; KS, Kaposi's sarcoma; US, ultrasound; HIV, human immunodeficiency virus; GI, endoscopy; HHV-8, human herpesvirus-8.

–: usually not.

+: usually yes.

++: mandatory.

±: according to symptoms.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2018.12.036>.

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