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

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**Corresponding author : Celeste Lebbé TEXT (3632 WORDS) ABSTRACT (222 WORDS)**

## **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 localized lesions, several local therapies have been developed without randomized 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 and disseminated KS: the recommended first line agents are pegylated liposomal doxorubicin (PLD) and paclitaxel. In classic KS, PLD or low dose interferon-alfa 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 m-TOR inhibitors are used. Follow-up schedules for patients with KS disease depend on aggressiveness of the disease.

## **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) in order 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 this 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 specialties 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.

## **METHODS**

To construct this EDF-EADO-EORTC guideline, a PubMed search with the terms "Kaposi's sarcoma", "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 \(http://www.ncbi.nlm.nih.gov/pubmed\)](http://www.ncbi.nlm.nih.gov/pubmed), [Google \(https://www.google.com\)](https://www.google.com), and [Embase \(https://www.embase.com\)](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, EORTC in several rounds, before producing the final version.

The present guidelines contains 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.

## **DEFINITION**

Kaposi's sarcoma (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 recognized 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]..

## **EPIDEMIOLOGY**

*Classic or Mediterranean KS (CKS)*

-Incidence:

CKS incidence is higher in mediterranean countries compared to 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 standardized incidence of 1.58 / 100,000 inhabitants per year in Sardinia between 1977 and 1991 [3].

Classic KS predominates in men with a sex ratio of 2 to 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].

#### -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 classic KS 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].

#### -Mortality

Due to its slow progression and indolent biologic behavior, 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].

### *Epidemic KS*

#### -Incidence

The incidence of epidemic KS has decreased worldwide since 1995 due to the institution of combination antiretroviral therapy (cART) with a standardized incidence ratio (SIR) 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 subsaharan Africa [21, 22].

#### -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].

#### -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].

#### -Post transplant KS

KS prevalence after organ transplantation parallels the overall prevalence of HHV-8 infection in the different countries: high ( $\geq 50\%$ ) HHV-8 prevalence in sub-Saharan Africa, intermediate HHV-8 seroprevalence (10% to 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].

#### -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/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].

#### -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 similar to overall survival in kidney transplant recipients [30]

## **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]. Lymphedema 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 colors (purple, yellow-green, blue and red) of vascular tumors [32]. Cutaneous distribution and severity, mucosal, nodal and visceral involvement e.g., lung, gastro-intestinal, bone and liver involvement, depend on the type of KS as summarized in Table 1. CKS has as a rule an indolent behaviour whereas epidemic and post transplant KS may be extensive and life-threatening.

## **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 characterized 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 characterized 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 localization 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 since it is specific of KS [35, 36].

### **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 PCR are available on an individual basis [31]...

#### *-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 sero-epidemiological studies but their usefulness in clinical daily practice is debated [31].

#### *-PCR*

PCR-based methods may be successfully used in order 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 tumor 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].

### **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 signaling pathways involved in angiogenesis and vascular differentiation [38, 39]. KS tumors 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].

## **PROGNOSIS -STAGING WORKUP- CLASSIFICATION**

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

*-Staging classification and workup:*

The only validated staging classification is for AIDS-associated KS. The AIDS Clinical trials Group (ACTG) Oncology Committee has elaborated a staging system in the pre-cART era, which includes measurement of the disease extent as localized 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 HAART, 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 classic KS, endemic KS and post-transplant KS. Patient management should distinguish 3 situations:

**localized non aggressive, locally aggressive, and disseminated KS.**

For classic KS, 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].

## **TREATMENT**

### *Local therapies*

Localized, symptomatic lesions can be treated using local approaches which are described below. There is no randomized 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 standardized classification systems for disease activity and clinical outcomes. The main studies are summarized in supplementary Table 1.

### *Physical agents*

#### - 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 to 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).

#### - Surgical excision

Surgical excision is grievied 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].

#### - Cryosurgery and Laser

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

#### *Local or intralesional chemical or immune modifying agents*

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

Intralesional vincristine was also used for classic KS 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 tumoral cells. In several prospective trials, electroporation associated with intravenous bleomycin (15,000 IU/m<sup>2</sup>) infusion showed complete response in about 65 to 89% of cases after 1-3 sessions [59] [60] [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].

#### *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 relies 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 summarized in supplementary Table 2. In classic KS 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 doxorubicine and paclitaxel.

-Pegylated liposomal doxorubicin

Pegylated liposomal doxorubicin (PLD) 20mg/m<sup>2</sup> every 3 weeks allows a best overall response rate of 76% in HIV-related-KS in association with cART and 71% to 100% in classic KS. The median duration of response is around 5 months in HIV-related KS and 25 months in classic KS [64]. The safety profile is good with around 5% grade 4 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. Pegylated liposomal doxorubicin is approved as first line therapy of HIV-related KS.

- Paclitaxel

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 to PLD (20 mg/m<sup>2</sup> every 3 weeks) in a randomized trial and showed comparable median progression free survival (17.5 versus 12.2 months, p=0.66) with more grade 3-5 toxicity for PCT, particularly more grade 4 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 80mg/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) [75]. (Level of evidence: 3; grade of recommendation: 0).

#### -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 classic KS with a very good rate of partial response in 71 to 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 anthracyclin. 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 dependant 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].

#### - Anti-angiogenic agents (Pomalidomide/Lenalidomide/Bevacizumab)

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

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

### **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.

#### *HIV related KS*

Combination antiretroviral therapy (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 (NNRTIs); protease inhibitors (PIs); integrase inhibitors (INI); fusion inhibitors (IFs); 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 individualized 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 immune reconstitution inflammatory syndrome (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, tumors may recur and patients often require additional therapies. Chronic administration of cytotoxic agents is poorly tolerated and in this setting, drugs like pomalidomide/lenalidomide may be discussed.

### *Post-transplant KS*

In the management of post-transplant KS, tapering down immunosuppressive therapy to the lowest possible level and switching to 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 since its use is associated with higher rejection risk.

### *Classic and endemic KS*

Aggressive forms characterized by lymph node and/or visceral involvement, severe edema, local complications or rapid extension require systemic treatment which is poorly codified [84]. The first options are generally based on the use of liposomal anthracyclins 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].

## **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 according to 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 done 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 to 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.

TABLES

**Table 1 Clinical features 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% [30, 91]	20 to 50% [30, 91]	20-40% [91] [30]

**Table 2 Prognostic factors of KS**

	<b>Prognostic factors</b>
<b>Classic/endemic KS</b> [86] Level of evidence 3	<ul style="list-style-type: none"> <li>- Immunosuppression</li> <li>- older age</li> </ul>
<b>AIDS-associated KS</b> [89, 92] Level of evidence 2	<ul style="list-style-type: none"> <li>- age ≥ 50 years</li> <li>- occurrence of KS at or after AIDS onset</li> <li>- immune status (CD4 counts)</li> <li>- Detectable HHV8 viremia</li> <li>- presence of systemic symptoms</li> <li>- having another AIDS-associated illness at the same time</li> </ul>

<b>Post transplant KS</b> Level of evidence 3	Not formally investigated. Prognosis relies on the feasibility of minimizing immunosuppression and not on KS extension
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**Table 3 AIDS\_Related KS. AIDS Clinical Trials Group Staging Classification [43]**

	Good prognosis (0)	Poor prognosis (1)
	(Any of the following)	(Any of the following)
Tumor (T)	Confined to skin and/or lymph nodes and/or minimal oral disease [ <i>Note: Minimal oral disease is non-nodular KS confined to the palate.</i> ]	Tumor-associated edema or ulceration
		Extensive oral KS
		Gastrointestinal KS
		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 <i>opportunistic infections</i> (OIs) or thrush	History of OIs and/or thrush
	No “B” symptoms [ <i>Note: “B” symptoms are unexplained fever, night sweats, &gt;10%</i>	“B” symptoms present

	<i>involuntary weight loss, or diarrhea persisting &gt;2 weeks.]</i>	
	Performance status ≥70 (Karnofsky)	Performance status <70
		Other HIV-related illness (e.g., neurological disease or lymphoma)

**Table 4. Proposed staging workup (good clinical practice)**

	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 scan: computerized tomography

Abdominal US: abdominal ultrasound

GI endoscopy: gastro intestinal endoscopy

- : usually not

+ : usually yes

++ mandatory

+/- : according to symptoms

**Table 5: Proposed follow-up (recommendation based on clinical practice)**

	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	+/-	+/-	+/-

- : usually not

+ : usually yes

++: mandatory

+/- : according to symptoms

**Conflict of Interest:**

Pr. Dummer has a consulting or advisory role for Amgen, BMS, MSD, Roche, Novartis, Pierre-Fabre, Sanofi, Takeda, Sun Pharma. Pr. Perris has nothing to disclose. Pr. Hoeller has consulting and speaker role for Amgen, BMS, MSD, Novartis, Pierre-Fabre, Roche. Pr. Zalaudek has nothing to disclose. Pr. Spano has consulting role for Roche, MSD, is in the board of Pfizer, Lilly, Astra Zeneca, Leo Pharma, Teva, participates in a symposium of Pfizer, BMS, Pierre-Fabre Oncology, Astra Zeneca, Leo Pharma, Janssen, 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, Regeneron, received a grant from BMS, Roche, Novartis, Pfizer. Pr. Battistella has consulting role from BMS, Innate Pharma, Leo Pharma, Takeda, Roche and received a research grant from Takeda. Pr. Forsea received personal fees from Novartis, Amgen, and non-Financial support from Leo Pharma, Amgen. Pr. Bylaite-Bucinskiene has nothing to disclose. Pr. Harwood received honoraria from Sanofi, Novartis, participate in commercial clinical trial from Pellepharm, Novartis, received grant from Novartis and received supply of medication for 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, Sanofi and received grant from BMS, Novartis, Roche. Pr. Eggermont participates in advisory board of Actelion, Agenus, Bayer, BMS, Frobion, HaliDX, Incyte, ISApharmaceuticals, MedImmune, Merck GmbH, MSD, Nektar, Novartis, Polynoma, Regeneron, Roche, Sellas, Sanofi, Theranovir, and participates in DMC from CellDex, Pfizer, Novartis. Pr. Kandolf Sekulovic received speakers's fees, travel, expenses from MSD, Roche, Novartis, BMS, Pfizer and non-financial support from MSD, Roche, Novartis, BMS, Pfizer. Pr. Grob has advisory role for BMS, MSD, Novartis, Roche, Pierre-Fabre, Amgen, Sun pharma, Merck, Pfizer, Sanofi, Sandoz. Pr. Del Marmol has nothing to disclose. Pr. Malvey has a consulting role for Amgen, Pierre-Fabre, Roche and participate in educational activities from Amgen, Pierre-Fabre, Roche. Pr. Olah has nothing to disclose. Pr. Pages has nothing to disclose. Pr. Lebbe has consulting role for Amgen, BMS, MSD, Roche, Novartis, Pierre-Fabre, Sanofi, Merck Serono and received grants from BMS, MSD, Roche, Novartis.

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