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**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**

# **Kaposi Sarcoma**

Version 2.2025 — January 14, 2025

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# NCCN Guidelines Version 2.2025

## Kaposi Sarcoma

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Φ Infectious diseases	¶ Surgery/Surgical oncology
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## Kaposi Sarcoma

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**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#).

**NCCN Categories of Preference:**  
All recommendations are considered appropriate.

[See NCCN Categories of Preference](#).

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# NCCN Guidelines Version 2.2025

## Kaposi Sarcoma

### Updates in Version 2.2025 of the NCCN Guidelines for Kaposi Sarcoma from Version 1.2025 include:

- [KS-F 3 of 4](#)
- Footnote k added: Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

### Updates in Version 1.2025 of the NCCN Guidelines for Kaposi Sarcoma from Version 2.2024 include:

#### Global

- References were updated throughout the Guidelines.
- "AIDS" has been replaced by "HIV" where appropriate.

#### KS-1

- Diagnosis
  - Essential, bullet 1 revised: Review of ~~all adequate~~ slides with ~~at least one from~~ paraffin block representative of the tumor by a pathologist with expertise in the diagnosis of Kaposi sarcoma.
- Workup
  - Essential
    - Bullet 1, History and physical examination
      - Sub-bullet 1 revised: Including history of additional ~~immunosuppression~~ immunosuppressive disease or therapy, such as transplant/local or systemic glucocorticoids.
      - Sub-bullet 2 revised: Including complete skin, oral, and lymph node examinations, and ~~evaluation documentation~~ of edema.
    - Essential Useful in selected cases
      - Bullet 1 moved from Essential: In patients of childbearing potential if chemotherapy or radiation therapy (RT) planned: pregnancy testing.
      - Bullet 9 added: For PWH, begin discussions regarding the possible need to modify ART due to DDIs and the need to involve an HIV specialist in care decisions. See Principles of Systemic Therapy and Drug-Drug Interactions (HIV-B) in the NCCN Guidelines for Patients with HIV.
- Footnote a, second sentence modified: Involvement of an ~~infectious disease (ID)~~ HIV specialist to evaluate for coexisting OI is appropriate, especially with advanced immunosuppression.

#### KS-2

- First line therapy if symptomatic and/or cosmetically bothersome, options revised: ~~Topicals or Intralesional chemotherapy or Local therapy or RT Local excision or Cryotherapy or Systemic therapy or Clinical trial.~~
- Footnote h revised: ~~All PWH who have limited cutaneous disease that is symptomatic (eg, edema, oral KS, or other manifestation that interfere with normal functions or activities) and/or cosmetically bothersome should receive ART with or without another first-line therapy.~~ Initiation of ART may result in immune reconstitution inflammatory syndrome (IRIS) within 3–6 months; IRIS is characterized by marked lesional swelling, increased tenderness, and peripheral edema. *Therefore, systemic KS-directed therapy should be initiated as soon as possible in all PWH who have symptomatic KS (eg, edema, oral KS, or other manifestation that interfere with normal functions or activities). In patients with limited cutaneous disease, KS-associated IRIS is an indication for urgent initiation of systemic KS therapy; signs of past IRIS may also be an indication for earlier initiation of systemic KS therapy.* ART should not be delayed or discontinued unless life-threatening IRIS develops. Reconstitution of immune function is important for obtaining and maintaining control or remission of KS. See Principles of Immune Reconstitution Inflammatory Syndrome (IRIS) (KS-C) (Also for KS-3)
- Footnote p, second sentence revised: If KS, evaluate for inadequate HIV control/~~ART failure~~ as a contributing factor to inadequate KS control and address possible change in ART in conjunction with an HIV specialist. (Also for KS-3)

#### KS-3

- Advanced cutaneous, oral, visceral, or nodal disease, bottom pathway revised: not *immediately* eligible for systemic therapy.
  - First-line therapy, bottom pathway revised: *Medical optimization and Consider* RT and Continue or initiate ART for PWH.
  - Not eligible for systemic therapy, pathway revised: *Consider RT or Best supportive care.*
  - Footnote r modified: Systemic therapy is preferred over RT as first-line therapy and relapsed/refractory therapy for disseminated disease whenever systemic therapy is feasible. *Although uncommon, considering performance status and medical comorbidities may preclude the use of upfront chemotherapy in some patients. Reversible medical issues should be addressed (eg, active infection requiring antibiotic or antiviral treatment; high-level HIV viremia requiring initiation/modification of ART) so that systemic therapy can be delivered as quickly as possible. If poor performance status is because of KS, systemic therapy should be considered because it may lead to an improvement in performance status.*



### Updates in Version 1.2025 of the NCCN Guidelines for Kaposi Sarcoma from Version 2.2024 include:

#### [KS-4](#)

- Surveillance
  - ▶ Bullet 1, quaternary bullet 2 revised: Including complete skin and oral examinations, and ~~documentation~~ *evaluation and monitoring* of edema
  - ▶ Bullet 2 modified: Photography of oral, conjunctival, and cutaneous lesions (with reference unit of measure in the picture) for ~~documentation~~ *evaluation* of extent of disease if change in disease is noted.

#### [KS-D](#)

- Local Therapy
  - ▶ Topical, bullet 1, sub-bullet revised: Apply ~~3–4~~ 2 times daily to affected skin sites; *increase to 3–4 times daily if tolerated*.
  - ▶ Cryotherapy, bullet added: Cryotherapy should be done by clinicians with expertise in cutaneous cancer cryotherapy.
  - ▶ Last header revised: For *local control* of small, *symptomatic* lesions (ie,  $\leq 1$  cm), the following may be considered: ~~for local control of symptomatic lesions~~
    - ◊ Bullet 1 revised: *Marginal* excision
    - ◊ Bullet 2 added: *Electrodesiccation and curettage*
    - ◊ Bullet 3, sub-bullet revised and moved above intralesional chemotherapy options: *Treatment schemas are listed below as a guide*. Other treatment schemas have been studied, with a variety of ~~vinblastine~~ *chemotherapy* concentrations, doses, administration volumes, frequencies of administration, and total doses/volumes administered. See Discussion for additional references and information.
    - ◊ Bullet 3, sub-bullet 2 added: Bleomycin as an option for intralesional chemotherapy
    - ◊ Bullet 3, sub-bullet 2, sub-bullet added: 1.5 to 3 units/mL solution with a dose of 0.5 unit per 0.5 cm<sup>2</sup> of lesion (volume given depends on the size of the lesion) every 3 to 4 weeks until response
    - ◊ Footnote a added: For larger lesions when systemic therapy is not feasible or effective, radiotherapy is preferred over excision.
- Footnote b added: Wide excision is not indicated.
- Reference 4 added: Poignonec S, Lachiver LD, Lamas G, et al. Intralesional bleomycin for acquired immunodeficiency syndrome-associated cutaneous Kaposi's sarcoma. Arch Dermatol 1995;131:228.

#### [KS-E](#)

- Principles of Radiation Therapy
  - ▶ General Treatment Information
    - ▶ Tertiary bullet revised: Various dosing schemas may be used. Lower *total* doses are preferred for smaller and more superficial lesions *and palliative situations*. Higher doses may be preferred for more extensive, deeply invasive lesions, *or when a more durable local response is desired*.
- Table: row 1, column 2 revised: ~~40–8~~ 9.6–14.4 Gy
- Footnote a added: BED is a measure of the radiosensitivity of the tissue, with BED10 denoting the estimated effective dose to rapidly growing tumor tissue and BED3 denoting the estimated dose to normal tissue (organs at risk).

#### [KS-F \(1 of 4\)](#)

- Systemic Therapy
  - ▶ Subsequent systemic therapy options revised: (also for table on KS-F [2 of 4])
    - ◊ Headers removed:
      - Preferred Regimen
      - Other Recommended Regimens
      - Preference stratification for subsequent therapy options was changed.
    - ◊ Useful in certain circumstances, regimens revised:
      - ◊ *Nivolumab ± ipilimumab + nivolumab (for classic KS)*
      - ◊ *Pembrolizumab (for endemic and classic KS)*
- Footnote g, second sentence added: If the patient has a history of KSHV-associated diseases, ICIs should be used with caution and with consideration of more frequent monitoring for signs and symptoms of KICS or MCD. See NCCN Guidelines for Cancer in People with HIV, Principles of Systemic Therapy and Drug-Drug Interactions. (Also for KS-F [3 of 4])
- Footnote removed: Pomalidomide has been U.S. Food and Drug Administration (FDA) approved for the treatment of adult patients with AIDS-related KS after failure of highly active ART or in patients with KS with no HIV.

#### [KS-F \(2 of 4\)](#)

- Useful in certain circumstances, regimen and dosing schedule added: Nivolumab, 480 mg IV every 4 weeks.





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## Kaposi Sarcoma

### DIAGNOSIS

#### ESSENTIAL:

- Review of adequate slides from paraffin block representative of the tumor by a pathologist with expertise in the diagnosis of Kaposi sarcoma (KS)
  - Rebiopsy if non-diagnostic
- Histopathology review of adequate biopsy (ie, skin punch, incisional, excisional)
- Adequate immunophenotyping to establish diagnosis
- Immunohistochemistry (IHC) panel: Kaposi sarcoma-associated herpesvirus (KSHV; human herpesvirus 8 [HHV-8]), LANA-1

#### USEFUL IN CERTAIN CIRCUMSTANCES:

- IHC: CD31 and CD34 if unclear whether the tumor has a vascular origin
- Encourage additional biopsy of nodal or visceral sites if a coexisting disorder is suspected (ie, infection, lymphoma, multicentric Castleman disease [MCD])

### WORKUP

#### ESSENTIAL:

- History and physical examination
  - Including history of additional immunosuppressive disease or therapy, such as transplant/local or systemic glucocorticoids
  - Including complete skin, oral, and lymph node examinations, and evaluation of edema
- Complete blood count (CBC), differential, and comprehensive metabolic panel
- Human immunodeficiency virus (HIV) screening and/or diagnostic testing<sup>a</sup>
- Photography of oral, conjunctival, and cutaneous lesions (with reference unit of measure in the picture) for evaluation and monitoring of extent of disease

#### USEFUL IN SELECTED CASES:

- In patients of childbearing potential if chemotherapy or radiation therapy (RT) planned: pregnancy testing
- Evaluation<sup>a</sup> for suspected opportunistic infections (OIs)
- In the setting of advanced cutaneous, oral, visceral, or nodal involvement: stool hemocult
- In the setting of advanced cutaneous, oral, visceral, or nodal disease, or any pulmonary symptoms: chest x-ray<sup>b</sup>
- If unexplained pulmonary symptoms or abnormalities on chest x-ray: chest CT with contrast<sup>b</sup> and bronchoscopy
- If gastrointestinal (GI) symptoms or positive hemocult: abdomen/pelvis CT with contrast<sup>b</sup> or MRI with and without contrast<sup>b</sup> and esophagogastroduodenoscopy (EGD)/colonoscopy
- If concerns for coexisting KSHV-associated inflammatory cytokine syndrome (KICS), MCD, or KSHV+ lymphoma, or other KSHV-associated disease: FDG-PET/CT scan<sup>b</sup> and/or lab workup<sup>c</sup>
- If anthracycline planned or suspected pericardial effusion: transthoracic echocardiogram
- For PWH, begin discussions regarding the possible need to modify ART due to DDIs and the need to involve an HIV specialist in care decisions. See [Principles of Systemic Therapy and Drug-Drug Interactions \(HIV-B\) in the NCCN Guidelines for Patients with HIV](#).

### KS STAGE<sup>d</sup>

Limited cutaneous disease

First-Line Therapy  
[\(KS-2\)](#)

Advanced cutaneous, oral, visceral, or nodal disease

First-Line Therapy  
[\(KS-3\)](#)

<sup>a</sup> All patients who are HIV seropositive should have recent T-cell subsets, including quantitative CD4+ T-cell count and HIV viral load to assess immune function and HIV control ([Discussion](#)). Involvement of an HIV specialist to evaluate for coexisting OI is appropriate, especially with advanced immunosuppression.

<sup>b</sup> Imaging should be directed by symptoms or findings concerning for visceral or bone involvement as well as coexisting KICS, MCD, or KSHV+ lymphoma and can include whole body FDG-PET/CT. See [NCCN Guidelines for B-Cell Lymphomas \(CD-1\)](#).

<sup>c</sup> Useful in patients with clinical features (ie, fever, dyspnea, effusions) concerning for KICS or KSHV-associated MCD: C-reactive protein, KSHV serum viral load, serum protein electrophoresis (SPEP), interleukin (IL)-6, or IL-10.

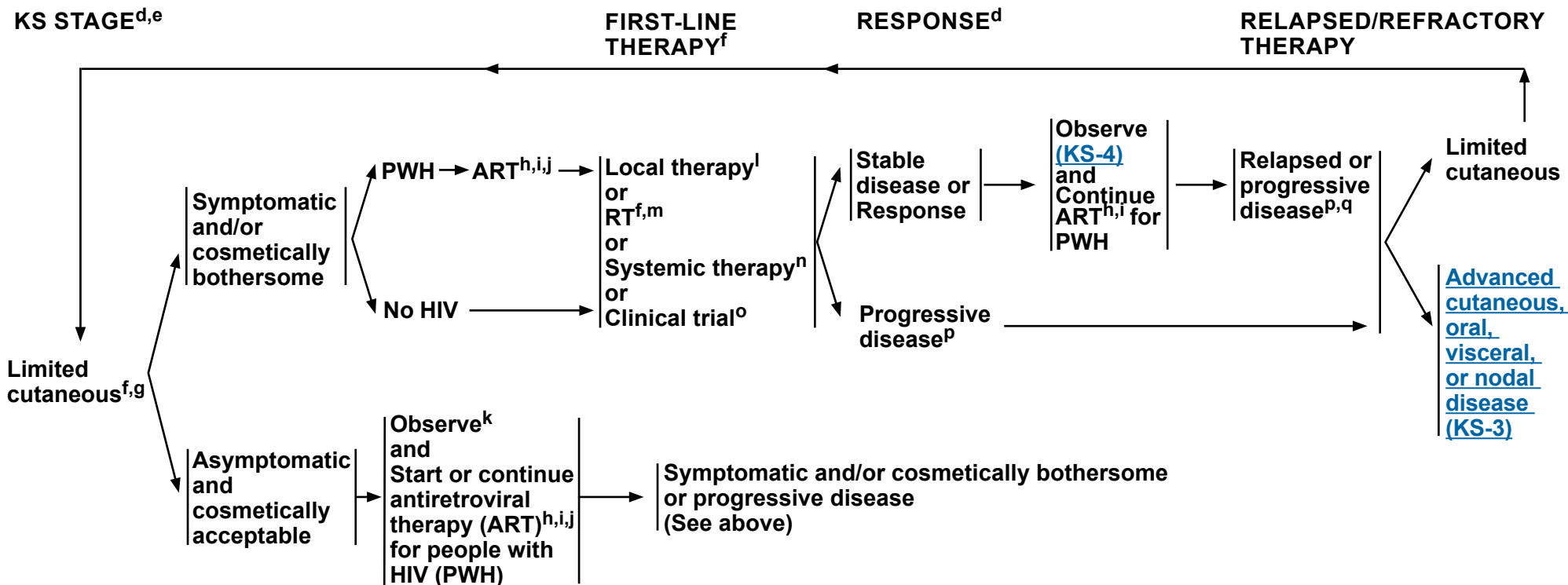
<sup>d</sup> See [Staging Classification for KS \(KS-A 1 of 2\)](#) and [Response Definitions for KS \(KS-A 2 of 2\)](#).

**Note:** All recommendations are category 2A unless otherwise indicated.



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## Kaposi Sarcoma



<sup>d</sup> See [Staging Classification for KS \(KS-A 1 of 2\)](#) and [Response Definitions for KS \(KS-A 2 of 2\)](#).

<sup>e</sup> Oncology and HIV clinicians, along with both an oncology pharmacist and HIV pharmacist, if available, should review proposed cancer therapy, supportive care medications, and ART for possible drug-drug interactions (DDIs) and overlapping toxicities prior to initiation. Co-management by an oncologist and an HIV clinician is recommended for the duration of therapy. See [NCCN Guidelines for Cancer in People with HIV](#).

<sup>f</sup> [Principles and Goals of Therapy \(KS-B\)](#).

<sup>g</sup> There is no agreed upon definition for limited cutaneous disease, but some trials have used inclusion criteria such as 5 index lesions or <5% body surface area involvement as the threshold. Clinical judgment is required.

<sup>h</sup> Initiation of ART may result in immune reconstitution inflammatory syndrome (IRIS) within 3–6 months; IRIS is characterized by marked lesional swelling, increased tenderness, and peripheral edema. Therefore, systemic KS-directed therapy should be initiated as soon as possible in all PWH who have symptomatic KS (eg, edema, oral KS, or other manifestation that interfere with normal functions or activities). In patients with limited cutaneous disease, KS-associated IRIS is an indication for urgent initiation of systemic KS therapy; signs of past IRIS may also be an indication for earlier initiation of systemic KS therapy. ART should not be delayed or discontinued unless life-threatening IRIS develops. Reconstitution of immune function is important for obtaining and maintaining control or remission of KS. See [Principles of Immune Reconstitution Inflammatory Syndrome \(IRIS\) \(KS-C\)](#).

<sup>i</sup> Glucocorticoids in any formulation should be avoided due to their association with KS progression. However, in cases of life-threatening conditions, their use may be considered.

<sup>j</sup> Patients who are only on ART should be reassessed within 4 weeks, particularly to monitor for KS-IRIS.

<sup>k</sup> Rapid progression during observation may be an indication for initiation of therapy.

<sup>l</sup> [Local Therapy \(KS-D\)](#).

<sup>m</sup> [Principles of Radiation Therapy \(KS-E\)](#).

<sup>n</sup> [Systemic Therapy \(KS-F\)](#).

<sup>o</sup> [clinicaltrials.gov](#).

<sup>p</sup> If progressive, relapsed, or refractory disease, consider biopsy of lesions since they may be areas of post-inflammatory pigment and/or mimickers of KS. If KS, evaluate for inadequate HIV control as a contributing factor to inadequate KS control and address possible change in ART in conjunction with an HIV specialist. See [NCCN Guidelines for Cancer in People with HIV](#).

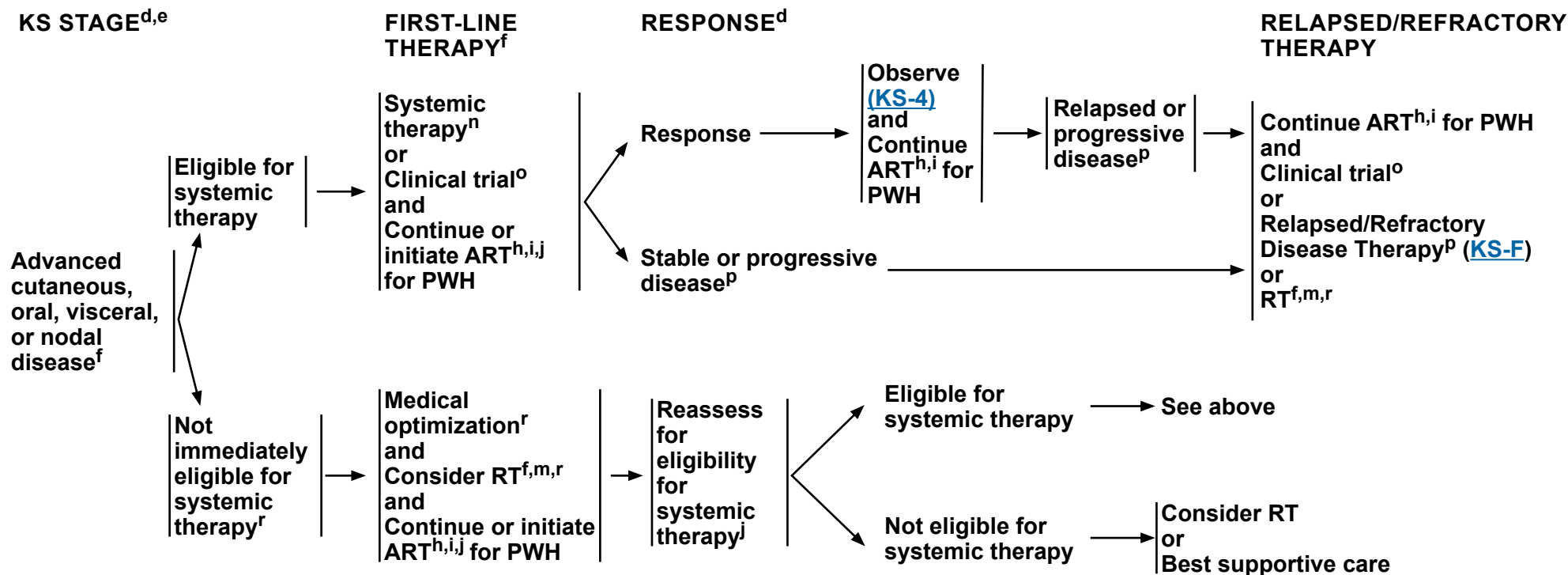
<sup>q</sup> If after initial response to therapy, KS relapses or progresses, repeat use of previously effective therapy may be considered, particularly if response was durable.

**Note: All recommendations are category 2A unless otherwise indicated.**



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<sup>d</sup> See [Staging Classification for KS \(KS-A 1 of 2\)](#) and [Response Definitions for KS \(KS-A 2 of 2\)](#).

<sup>e</sup> Oncology and HIV clinicians, along with both an oncology pharmacist and HIV pharmacist, if available, should review proposed cancer therapy, supportive care medications, and ART for possible DDIs and overlapping toxicities prior to initiation. Co-management by oncologist and HIV clinician is recommended for the duration of therapy. See [NCCN Guidelines for Cancer in People with HIV](#).

<sup>f</sup> [Principles and Goals of Therapy \(KS-B\)](#).

<sup>h</sup> Initiation of ART may result in IRIS within 3–6 months; IRIS is characterized by marked lesional swelling, increased tenderness, and peripheral edema. Therefore, systemic KS-directed therapy should be initiated as soon as possible in all PWH who have symptomatic KS (eg, edema, oral KS, or other manifestation that interfere with normal functions or activities). In patients with limited cutaneous disease, KS-associated IRIS is an indication for urgent initiation of systemic KS therapy; signs of past IRIS may also be an indication for earlier initiation of systemic KS therapy. ART should not be delayed or discontinued unless life-threatening IRIS develops. Reconstitution of immune function is important for obtaining and maintaining control or remission of KS. See [Principles of Immune Reconstitution Inflammatory Syndrome \(IRIS\) \(KS-C\)](#).

<sup>i</sup> Glucocorticoids in any formulation should be avoided due to their association with KS progression. However, in cases of life-threatening conditions, their use may be considered.

<sup>j</sup> Patients who are only on ART should be reassessed within 4 weeks, particularly to monitor for KS-IRIS.

<sup>m</sup> [Principles of Radiation Therapy \(KS-E\)](#).

<sup>n</sup> [Systemic Therapy \(KS-F\)](#).

<sup>o</sup> [clinicaltrials.gov](#).

<sup>p</sup> If progressive, relapsed, or refractory disease, consider biopsy of lesions since they may be areas of post-inflammatory pigment and/or mimickers of KS. If KS, evaluate for inadequate HIV control as a contributing factor to inadequate KS control and address possible change in ART in conjunction with an HIV specialist. See [NCCN Guidelines for Cancer in People with HIV](#).

<sup>r</sup> Systemic therapy is preferred over RT as first-line therapy and relapsed/refractory therapy for disseminated disease whenever systemic therapy is feasible. Although uncommon, performance status and medical comorbidities may preclude the use of upfront chemotherapy in some patients. Reversible medical issues should be addressed (eg, active infection requiring antibiotic or antiviral treatment; high-level HIV viremia requiring initiation/modification of ART) so that systemic therapy can be delivered as quickly as possible. If poor performance status is because of KS, systemic therapy should be considered because it may lead to an improvement in performance status.

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### SURVEILLANCE

- For patients not requiring active therapy and with no signs of progression
  - ▶ Follow-up periodically based on response to therapy and, if applicable, degree of HIV viremia and immune reconstitution
    - ◊ History and physical examination
      - Including history of additional immunosuppression such as transplant/glucocorticoids
      - Including complete skin and oral examinations, and evaluation and monitoring of edema
    - ◊ CBC, differential, comprehensive metabolic panel
    - ◊ PWH
      - T-cell subsets (CD4+ T-cell count) and HIV viral load
      - Assess ART compliance
- Photography of oral, conjunctival, and cutaneous lesions (with reference unit of measure in the picture) for evaluation of extent of disease if change in disease is noted
- If signs and symptoms concerning for visceral involvement or prior to new therapy if progression/refractory disease or if change in disease is noted, the following are indicated depending on the clinical circumstances<sup>b</sup>:
  - ▶ Evaluation for suspected OIs
  - ▶ In the setting of advanced cutaneous, oral, visceral, or nodal involvement: stool hemocult
  - ▶ In the setting of advanced cutaneous, oral, visceral, or nodal disease: chest x-ray<sup>b</sup>
  - ▶ If unexplained pulmonary symptoms or abnormalities on chest x-ray: chest CT with contrast<sup>b</sup> and bronchoscopy
  - ▶ If GI symptoms or positive hemocult: abdomen/pelvis CT<sup>b</sup> with contrast or MRI with and without contrast<sup>b</sup> and EGD/colonoscopy
  - ▶ If concerns for coexisting KICS, MCD, or KSHV+ lymphoma, or other KSHV-associated disease: FDG-PET/CT<sup>b</sup> and/or lab workup<sup>c</sup>
  - ▶ The diagnosis of KICS ideally requires excisional biopsy of lymphadenopathy to exclude MCD, if feasible
- As KSHV is not eradicated with treatment of KS, the risk for future KS persists even after complete remission.
- For PWH, optimization and monitoring of HIV control and immune function is important to minimize this risk. This risk depends on immune function and generally decreases with immune reconstitution. However, KS can persist, relapse, or present even in the setting of normal values of T-cell subsets. Less frequent (every 6–12 mo) oncology monitoring may be appropriate for selected patients with undetectable HIV viral loads, normal T-cell subsets, and stable KS for 2 or more years as long as the patient has regular follow-up with an HIV provider.

<sup>b</sup> Imaging should be directed by symptoms or findings concerning for visceral or bone involvement as well as coexisting KICS, MCD, or KSHV+ lymphoma and can include whole body FDG-PET/CT. See [NCCN Guidelines for B-Cell Lymphomas \(CD-1\)](#).

<sup>c</sup> Useful in patients with clinical features (ie, fever, dyspnea, effusions) concerning for KICS or KSHV-associated MCD: C-reactive protein, KSHV serum viral load, SPEP, IL-6, or IL-10.

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# NCCN Guidelines Version 2.2025

## Kaposi Sarcoma

### STAGING CLASSIFICATION FOR KS<sup>a</sup>

	Good risk (all of the following)	Poor risk (any of the following)
<b>Tumor, T</b>	<b>T0: Confined to skin and/or lymph nodes and/or minimal oral disease (non-nodular KS confined to palate)</b>	<b>T1: Tumor-associated edema or ulceration Extensive oral KS Gastrointestinal KS KS in organs other than lymph nodes</b>
<b>Immune system, I<sup>1</sup></b>	<b>I0: CD4+ T-cell count ≥150/μL</b>	<b>I1: CD4+ T-cell count &lt;150/μL</b>
<b>Systemic disease, S</b>	<b>S0: No history of opportunistic infection or thrush No “B” symptoms<sup>2</sup> Karnofsky Performance Status ≥70</b>	<b>S1: History of opportunistic infection and/or thrush “B” symptoms present Karnofsky Performance Status &lt;70 Other HIV-related illness (eg, neurologic disease, lymphoma)</b>
<sup>1</sup> I stage has less prognostic value than T or S stages in patients on ART therapy. <sup>2</sup> “B” symptoms are unexplained fever, night sweats, >10% involuntary weight loss, or diarrhea persisting >2 weeks.		

<sup>a</sup> Adapted from Krown SE, Metroka C, Wernz JC. Kaposi’s sarcoma in the acquired immune deficiency syndrome: a proposal for uniform evaluation, response, and staging criteria. AIDS Clinical Trials Group Oncology Committee. J Clin Oncol 1989;7:1201-1207.

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# NCCN Guidelines Version 2.2025

## Kaposi Sarcoma

### RESPONSE DEFINITIONS FOR KS<sup>a</sup>

<b>Complete response (CR)</b>	<b>The absence of any detectable residual disease, including tumor-associated (local) edema, persisting for at least 4 weeks. Patients known to have had visceral disease should have restaging with appropriate endoscopic or radiographic procedures relevant to sites involved at baseline.</b>
<b>Partial response (PR)</b>	<p><b>No new mucocutaneous lesions, visceral sites of involvement, or the appearance or worsening of tumor-associated edema or effusions; AND</b></p> <ul style="list-style-type: none"> <li>▶ <b>A 50% or greater decrease in the number of all previous existing lesions lasting for at least 4 weeks;</b> OR</li> <li>▶ <b>Complete flattening of at least 50% of all previously raised lesions (ie, 50% of all previously nodular or plaque-like lesions become macules);</b> OR</li> <li>▶ <b>A 50% decrease in the sum of the products of the largest perpendicular diameters of at least 5 measurable lesions.</b></li> </ul> <p><b>NOTE: When there is residual tumor-associated edema or effusion, but disease otherwise meets criteria for complete response, response should be classified as "partial."</b></p>
<b>Stable disease (SD)</b>	<b>Any response that does not meet the criteria for progressive disease or PR.</b>
<b>Progressive disease (PD)</b>	<b>An increase of <math>\geq 25\%</math> in the size of pre-existing lesions and/or the appearance of new lesions or sites of disease and/or a change in the character of the skin or oral lesions from macular to plaque-like or nodular of <math>\geq 25\%</math>. If new or increasing tumor-associated edema or effusion develop, disease is considered to be progressive.</b>

<sup>a</sup> Adapted from Krown SE, Metroka C, Wernz JC. Kaposi's sarcoma in the acquired immune deficiency syndrome: a proposal for uniform evaluation, response, and staging criteria. AIDS Clinical Trials Group Oncology Committee. J Clin Oncol 1989;7:1201-1207.

**Note: All recommendations are category 2A unless otherwise indicated.**



### PRINCIPLES AND GOALS OF THERAPY

#### Principles of Therapy:

- Individual KS lesions may be distinct clones that arise due to the common risk factors of immunosuppression and persistent KSHV infection as opposed to metastases. Treatment of existing disease therefore may not prevent occurrence of future lesions.
- Optimization of immune function and avoidance of additional immunosuppression are critical to prevention of additional KS lesions and maintenance of response to therapy. For HIV-related KS, reconstitution of immune function and maintenance of viral suppression are important. Also, it is important to work with an HIV specialist to optimize suppression of HIV and reconstitution of immune function with ART.
  - ▶ Important examples of iatrogenic immunosuppression, which may promote KS, include not only systemic but local glucocorticoids (ie, inhaled, topical, intra-articular). Note that KS may flare in a remote location from the site of local glucocorticoids.
    - ◊ Glucocorticoids in any formulation should be avoided due to their association with KS progression.<sup>1-3</sup> However, in cases of life-threatening conditions, their use may be considered. Proceed with caution if using glucocorticoids or consult an HIV or KS specialist.
  - ▶ Patients requiring rituximab for treatment of non-Hodgkin lymphoma (NHL) with coexisting KS or MCD may develop flares of KS or incident KS. This may be mitigated by use of concurrent chemotherapy active against both KS and disease for which rituximab is prescribed (ie, doxorubicin).
- Persons with HIV-related KS, especially those with advanced immunosuppression, are at increased risk of OIs marrow suppression with neutropenic fever, or thrombocytopenic bleeding and should be monitored closely. It is important to collaborate with an HIV specialist to ensure adequate OI prophylaxis appropriate to CD4+ T-cell count (which may temporarily decrease with cytotoxic chemotherapy). Growth factor support may be needed to facilitate systemic therapy.
- Lymphedema and soft tissue infections: KS is often complicated by lymphedema with increased risk of cellulitis and deep tissue infections in affected limbs. Risk of severe lymphedema and delayed wound healing may be increased after radiation. Refer to a lymphedema specialist. In the setting of advanced cutaneous disease, radiation should be reserved for circumstances when systemic therapy is not feasible with the goal of palliation or short-term disease management until systemic therapy may be delivered. Note that treatment responses may be delayed in the context of significant lymphedema.

#### Goals of Therapy:

- PWH with limited cutaneous disease that is asymptomatic and cosmetically acceptable may be observed while starting or continuing ART with optimization of immune function and HIV viral suppression as above. Remissions or stable disease may occur with ART and optimization of immune function and HIV viral suppression alone.
- Patients with symptomatic or cosmetically bothersome disease should use minimally invasive and the least toxic therapy to control disease. When necessary, a limited number of cycles of systemic therapy (eg, 3–6) may be sufficient for those initiating or re-initiating ART.
- Patients with advanced symptomatic cutaneous, visceral, nodal, or oral disease should be treated with systemic therapy with the goal of reducing or reversing symptoms, lymphedema, or threat to organ function. Complete remissions are rare.
  - ▶ Treatment is typically continued until unacceptable toxicity or plateau in response; maintenance therapy beyond 2 cycles of systemic therapy after determination of plateau is not recommended. If response is then clinically acceptable, patients may be observed (while continuing ART, in PWH). Otherwise, alternative therapy should be initiated.

<sup>1</sup> Fernandez-Sanchez M, Iglesias MC, Ablanado-Terrazas Y, et al. Steroids are a risk factor for Kaposi's sarcoma-immune reconstitution inflammatory syndrome and mortality in HIV infection. *AIDS* 2016;30:909-914.

<sup>2</sup> Guo WX, Antakly T. AIDS-related Kaposi's sarcoma: evidence for direct stimulatory effect of glucocorticoid on cell proliferation. *Am J Pathol* 1995;146:727-734.

<sup>3</sup> Volkow PF, Cornejo P, Zinser JW, et al. Life-threatening exacerbation of Kaposi's sarcoma after prednisone treatment for immune reconstitution inflammatory syndrome. *AIDS* 2008;22:663-665.

**Note: All recommendations are category 2A unless otherwise indicated.**



### PRINCIPLES OF IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

#### CLINICAL PRESENTATION/DEFINITION<sup>1</sup>

- IRIS is characterized by first presentation or paradoxical worsening of pre-existing KS infection following ART initiation.
- Typically occurs within 3 months of ART initiation, but possible to occur any time after starting ART.
- PWH with advanced KS not on ART at the time of presentation, should start systemic therapy as soon as possible after the initiation of ART to minimize the risk of severe KS-IRIS.
- The risk of IRIS is higher in patients with baseline low CD4 T-cell counts and high HIV viral loads.<sup>2</sup>
- Clinical manifestations may include development of new lesions or enlargement of existing lesions, worsening lymphadenopathy, or worsening edema. The clinical presentation of IRIS may be challenging to distinguish from the natural history of progressive disease.
- If IRIS is suspected, consult with an HIV specialist.

#### MANAGEMENT

- Treatment for KS-IRIS includes systemic chemotherapy and supportive measures; ART should not be discontinued.
- If the patient is on ART only: Symptomatic management; consider addition of systemic chemotherapy (see list of first-line options).
  - ▶ Consider thalidomide as an active agent against both KS and corticosteroid-refractory IRIS.
- If the patient is on ART and chemotherapy: Symptomatic management; consider modification of chemotherapy regimen if progressive.
- Avoid corticosteroids, which may exacerbate KS.
- Use of systemic chemotherapy for extensive disease prior to ART initiation may help prevent KS-IRIS, but this has not been systematically studied.

#### PROPOSED CRITERIA FOR DIAGNOSIS OF KS-IRIS<sup>3</sup>

KS-IRIS requires at least one major and one minor criterion:

##### Major Criteria

- New onset or enlargement of KS lesion and subsequent regression
- Painful lesions

##### Minor Criteria

- Decrease in plasma HIV RNA by  $>1 \log^{10}$  copies/mL
- Increased blood CD4 T-cell count after ART

<sup>1</sup> Letang E, Lewis JJ, Bower M, et al. Immune reconstitution inflammatory syndrome associated with Kaposi sarcoma: higher incidence and mortality in Africa than in the UK. *AIDS* 2013;27:1603-1613.

<sup>2</sup> Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at <https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv>. Accessed 9/6/2022.

<sup>3</sup> French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. *AIDS* 2004;18:1615-1627.

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### LOCAL THERAPY

#### Topical

- **Alitretinoin 0.1% gel<sup>1</sup>**
  - ▶ Apply 2 times daily to affected skin sites; increase to 3–4 times daily if tolerated
- **Imiquimod, 5% cream<sup>2</sup>**
  - ▶ Apply one sachet to up to 20 cm<sup>2</sup> of affected skin and cover with occlusive dressing for 8 hours three times per week; titrate frequency of application to effect and tolerability (up to once daily), with treatment breaks if tolerability issues occur.

#### Radiotherapy<sup>a</sup>

- [Principles of Radiation Therapy \(KS-E\)](#)

#### Cryotherapy

- Cryotherapy should be done by clinicians with expertise in cutaneous cancer cryotherapy.

#### For local control of small, symptomatic lesions, the following may be considered:

- **Marginal excision<sup>b</sup>**
- **Electrodesiccation and curettage**
- **Intralesional chemotherapy**
  - ◊ Pain from injection is common and may persist for several days. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be useful to relieve pain from injection.
  - ◊ Intralesional chemotherapy to plantar and palmar surfaces might be useful in selected cases, but should be approached with caution.
  - ◊ Treatment schemas are listed below as a guide. Other treatment schemas have been studied, with a variety of chemotherapy concentrations, doses, administration volumes, frequencies of administration, and total doses/volumes administered. See [Discussion](#) for additional references and information.
- ▶ **Vinblastine<sup>3</sup>**
  - ◊ 0.2 mg/mL solution with a volume of 0.1 mL per 0.5 cm<sup>2</sup> of lesion
- ▶ **Bleomycin<sup>4</sup>**
  - ◊ 1.5 to 3 units/mL solution with a dose of 0.5 unit per 0.5 cm<sup>2</sup> of lesion (volume given depends on the size of the lesion) every 3 to 4 weeks until response

#### Footnotes

<sup>a</sup> For larger lesions when systemic therapy is not feasible or effective, radiotherapy is preferred over excision.

<sup>b</sup> Wide excision is not indicated.

#### References

- <sup>1</sup> Bodsworth NJ, Bloch M, Bower M, et al. Phase III vehicle-controlled, multi-centered study of topical alitretinoin gel 0.1% in cutaneous AIDS-related Kaposi's sarcoma. *Am J Clin Dermatol* 2001;2:77-87.
- <sup>2</sup> Scharz NEC, Chevret S, Paz C, et al. Imiquimod 5% cream for treatment of HIV-negative Kaposi's sarcoma skin lesions: a phase I to II open-label trial in 17 patients. *J Am Acad Dermatol* 2008;58:585-591.
- <sup>3</sup> Epstein JB. Treatment of oral Kaposi sarcoma with intralesional vinblastine. *Cancer* 1993;71:1722-1725.
- <sup>4</sup> Poignonec S, Lachiver LD, Lamas G, et al. Intralesional bleomycin for acquired immunodeficiency syndrome-associated cutaneous Kaposi's sarcoma. *Arch Dermatol* 1995;131:228.

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### PRINCIPLES OF RADIATION THERAPY

#### • General Principles

- ▶ For most skin lesions, electrons or superficial x-rays can be used to deliver optimal dosimetry and minimize dose to underlying structures. To ensure sufficient dose is delivered for deeper or larger lesions, conformal photon therapy or mixed photon-electron treatment plans may be used. Intensity-modulated RT (IMRT) with or without image guidance may be useful for larger, deeper disease, or disease located anatomically adjacent to critical structures.
- ▶ The use of bolus may be necessary to achieve adequate skin dose.
- ▶ RT to plantar and palmar surfaces might be useful in selected cases. However, high doses should be approached with caution because of theoretical toxicity concerns like long-term wound healing, particularly in the setting of coexisting lymphedema.
- ▶ Risk of secondary cancer, severe or worsening lymphedema, and long-term wound healing complications may be increased after radiation; however, toxicity can be mitigated by utilizing lower-dose radiotherapy regimens. Caution should be exercised with the use of RT to sites of pre-existing lymphedema. In the setting of advanced cutaneous disease, radiation should be reserved for circumstances when systemic therapy is not feasible with the goal of palliation or short-term disease management until systemic therapy may be delivered.

#### • General Treatment Information

##### ▶ Dosing Prescription Regimen<sup>1,2,3</sup>

- ◊ Various dosing schemas may be used. Lower total doses are preferred for smaller and more superficial lesions and palliative situations. Higher doses may be preferred for more extensive, deeply invasive lesions, or when a more durable local response is desired. More fractionated regimens may be preferred for sites with adjacent radiosensitive structures, such as the oral cavity. Examples:

Fractionated Dose	Biologically Effective Dose [BED] <sup>10a</sup>	BED3
6–8 Gy in 1 fraction <sup>4</sup>	9.6–14.4 Gy	18–29 Gy
20 Gy in 5 fractions <sup>1,3</sup>	28 Gy	47 Gy
24 Gy in 12 fractions <sup>1</sup>	28.8 Gy	40 Gy
30 Gy in 10–15 fractions <sup>2,3</sup>	36–39 Gy	50–60 Gy
40 Gy in 20 fractions <sup>5</sup>	48 Gy	67 Gy

#### Footnote

<sup>a</sup> BED is a measure of the radiosensitivity of the tissue, with BED<sub>10</sub> denoting the estimated effective dose to rapidly growing tumor tissue and BED<sub>3</sub> denoting the estimated dose to normal tissue (organs at risk).

#### References

- <sup>1</sup> Singh NB, Lakier RH, Donde B. Hypofractionated radiation therapy in the treatment of epidemic Kaposi sarcoma – a prospective randomized trial. *Radiother Oncol* 2008;88:211-216.
- <sup>2</sup> Hauerstock D, Gerstein W, Vuong T. Results of radiation therapy for treatment of classic Kaposi sarcoma. *J Cutan Med Surg* 2009;13:18-21.
- <sup>3</sup> Kirova YM, Belembaogo E, Frikha H, et al. Radiotherapy in the management of epidemic Kaposi's sarcoma: a retrospective study of 643 cases. *Radiother Oncol* 1998;46:19-22.
- <sup>4</sup> Tsao MN, Sinclair E, Assaad D, et al. Radiation therapy for the treatment of skin Kaposi sarcoma. *Ann Palliat Med* 2016;5:298-302.
- <sup>5</sup> Stelzer KJ, Griffin TW. A randomized prospective trial of radiation therapy for AIDS-associated Kaposi's sarcoma. *Int J Radiat Oncol Biol Phys* 1993;27:1057-1061.

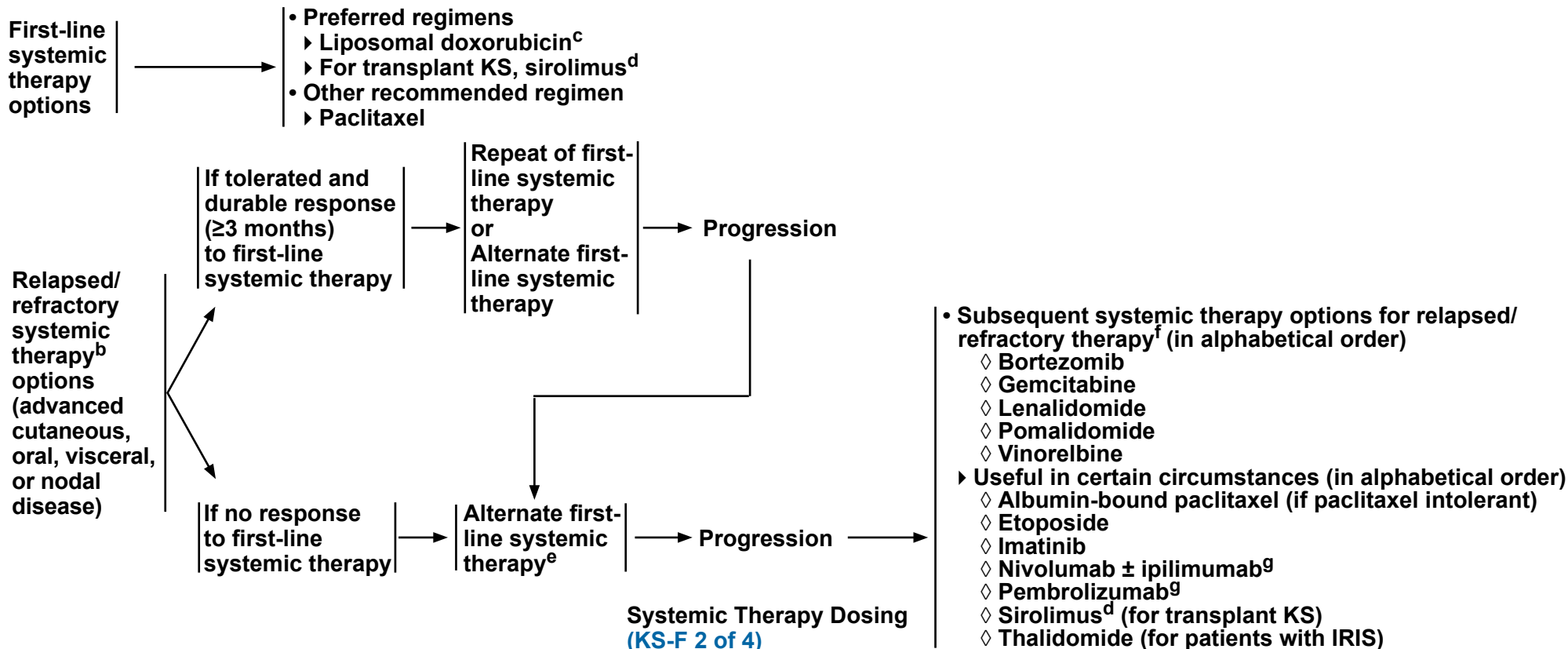
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# NCCN Guidelines Version 2.2025

## Kaposi Sarcoma

### SYSTEMIC THERAPY<sup>a</sup>



<sup>a</sup> [References for regimens on KS-F \(4 of 4\)](#).

<sup>b</sup> Consider repeating any prior systemic therapy that was tolerated and resulted in a durable response.

<sup>c</sup> Due to potential risk of cardiotoxicity, perform echocardiogram prior to initial course of liposomal doxorubicin and repeat periodically. Consider limiting lifetime dose per prescribing guidelines; however, other data suggest that the patients who need continued treatment may be safely treated beyond 1000 mg/m<sup>2</sup>.

<sup>d</sup> For KS associated with immunosuppression from solid organ transplant switching to sirolimus for immunosuppression may be sufficient for KS control and treatment. Systemic therapy given concurrently with sirolimus would be appropriate in more aggressive or advanced disease.

<sup>e</sup> If both first-line options have already been given, the patient should proceed to the subsequent systemic therapy options.

<sup>f</sup> Patients can continue through all treatment options listed, and treatments can be repeated if tolerated and response was durable (≥3 months). In select cases, best supportive care may be an appropriate option.

<sup>g</sup> Immune checkpoint inhibitors (ICIs) should not be used in patients with MCD or KICS due to the risk of flare of these conditions. If the patient has a history of KSHV-associated diseases, ICIs should be used with caution and with consideration of more frequent monitoring for signs and symptoms of KICS or MCD. See [NCCN Guidelines for Cancer in People with HIV, Principles of Systemic Therapy and Drug-Drug Interactions](#). See [Discussion](#).

**Note: All recommendations are category 2A unless otherwise indicated.**



# NCCN Guidelines Version 2.2025

## Kaposi Sarcoma

### SYSTEMIC THERAPY DOSING<sup>a,h</sup>

FIRST-LINE SYSTEMIC THERAPY DOSING	
<b>Preferred regimens</b> <ul style="list-style-type: none"> <li>• <b>Liposomal doxorubicin<sup>c</sup></b> <ul style="list-style-type: none"> <li>▶ 20 mg/m<sup>2</sup> IV every 2 to 3 weeks</li> </ul> </li> <li>• <b>Sirolimus (for transplant KS)</b> <ul style="list-style-type: none"> <li>▶ Loading dose 0.15 mg/kg PO followed by 0.04–0.06 mg/kg/day to maintain trough blood levels of 6–10 ng/mL or 2 mg PO daily (adjust to maintain trough levels of 6–10 ng/mL)</li> <li>▶ For PWH on ART, providers should consult with an infectious disease (ID) pharmacist prior to dosing sirolimus</li> </ul> </li> </ul>	<b>Other recommended regimen</b> <ul style="list-style-type: none"> <li>• <b>Paclitaxel</b> <ul style="list-style-type: none"> <li>▶ Premedication with dexamethasone may not be needed; if used, the dose should be minimized and tailored to patient needs.</li> <li>▶ Dose schedule options: <ul style="list-style-type: none"> <li>◊ 60 mg/m<sup>2</sup> IV weekly</li> <li>◊ 100 mg/m<sup>2</sup> IV every 2 weeks</li> <li>◊ 100 mg/m<sup>2</sup> IV every 3 weeks</li> <li>◊ 135 mg/m<sup>2</sup> IV every 3 weeks</li> </ul> </li> </ul> </li> </ul>

SUBSEQUENT SYSTEMIC THERAPY OPTIONS FOR RELAPSED/REFRACTORY THERAPY DOSING		
<ul style="list-style-type: none"> <li>• <b>Bortezomib</b> <ul style="list-style-type: none"> <li>▶ 1.6 mg/m<sup>2</sup> IV/SC on days 1, 8, and 15 of each 28-day cycle</li> </ul> </li> <li>• <b>Gemcitabine</b> <ul style="list-style-type: none"> <li>▶ 1000 mg/m<sup>2</sup> IV every 2 weeks</li> <li>▶ Or 1000 mg/m<sup>2</sup> IV on days 1 and 8 every 21 days</li> </ul> </li> <li>• <b>Lenalidomide<sup>i</sup></b> <ul style="list-style-type: none"> <li>▶ 25 mg/day PO for 21 days of each 28-day cycle</li> </ul> </li> <li>• <b>Pomalidomide<sup>i</sup></b> <ul style="list-style-type: none"> <li>▶ 4 or 5 mg/day PO for 21 days of each 28-day cycle<sup>j</sup></li> </ul> </li> <li>• <b>Vinorelbine</b> <ul style="list-style-type: none"> <li>▶ 30 mg/m<sup>2</sup> IV every 2 weeks</li> </ul> </li> </ul>	<b>Useful in certain circumstances (in alphabetical order)</b> <ul style="list-style-type: none"> <li>• <b>Albumin-bound paclitaxel (if paclitaxel intolerant)</b> <ul style="list-style-type: none"> <li>▶ 100 mg IV on days 1, 8, and 15 of each 28-day cycle</li> </ul> </li> <li>• <b>Etoposide</b> <ul style="list-style-type: none"> <li>▶ 50 mg/day PO for 7 days of each 14-day cycle. After 2 cycles, escalate dose to 100 mg/day PO for 7 days of each 14-day cycle in patients without PR or CR and no toxicity &gt;Grade 2. Dose can be further escalated to 150 mg/day based on tolerance and response</li> </ul> </li> <li>• <b>Imatinib</b> <ul style="list-style-type: none"> <li>▶ 400 mg/day PO</li> </ul> </li> <li>• <b>Nivolumab + ipilimumab<sup>g</sup></b> <ul style="list-style-type: none"> <li>▶ Nivolumab 240 mg IV every 2 weeks and ipilimumab 1 mg/kg IV every 6 weeks</li> </ul> </li> <li>• <b>Nivolumab<sup>k</sup></b> <ul style="list-style-type: none"> <li>▶ 480 mg IV every 4 weeks</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• <b>Pembrolizumab<sup>g</sup></b> <ul style="list-style-type: none"> <li>▶ 200 mg IV every 3 weeks for up to 6 months</li> </ul> </li> <li>• <b>Sirolimus (for transplant KS)</b> <ul style="list-style-type: none"> <li>▶ Loading dose 0.15 mg/kg PO followed by 0.04–0.06 mg/kg/day to maintain trough blood levels of 6–10 ng/mL or 2 mg PO daily (adjust to maintain trough levels of 6–10 ng/mL).</li> <li>▶ For PWH on ART, providers should consult with an ID pharmacist prior to dosing sirolimus</li> </ul> </li> <li>• <b>Thalidomide (for patients with IRIS)<sup>i</sup></b> <ul style="list-style-type: none"> <li>▶ 200 mg/day orally (starting dose, titrated to effect and tolerability)</li> </ul> </li> </ul>

Note: All recommendations are category 2A unless otherwise indicated.

[Footnotes on KS-F 3 of 4](#)  
[References on KS-F 4 of 4](#)



### SYSTEMIC THERAPY FOOTNOTES

<sup>a</sup> [References for regimens on KS-F \(4 of 4\).](#)

<sup>c</sup> Due to potential risk of cardiotoxicity, perform echocardiogram prior to initial course of liposomal doxorubicin and repeat periodically. Consider limiting lifetime dose per prescribing guidelines; however, other data suggest that the patients who need continued treatment may be safely treated beyond 1000 mg/m<sup>2</sup>.

<sup>g</sup> Immune checkpoint inhibitors should not be used in patients with MCD or KICS due to the risk of flare of these conditions. If the patient has a history of KSHV-associated diseases, ICIs should be used with caution and with consideration of more frequent monitoring for signs and symptoms of KICS or MCD. See [NCCN Guidelines for Cancer in People with HIV, Principles of Systemic Therapy and Drug-Drug Interactions. See Discussion.](#)

<sup>h</sup> For PWH, see [NCCN Guidelines for Cancer in People with HIV, Principles of Systemic Therapy and Drug-Drug Interactions \(HIV-B\).](#)

<sup>i</sup> Patients of childbearing potential treated with pomalidomide, lenalidomide, or thalidomide require effective contraception if participating in sexual activity that could result in pregnancy. Refer to the risk evaluation and mitigation (REMS) program for the specific therapy.

<sup>j</sup> The clinical trial for pomalidomide used a dose of 5 mg/day. However, pomalidomide is provided in a 4-mg dose and the NCCN Panel believes that this is a sufficient dose.

<sup>k</sup> Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

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### SYSTEMIC THERAPY REFERENCES

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#### Bortezomib

Reid E, Suazo A, Lensing SY, et al. Pilot trial AMC-063: Safety and efficacy of bortezomib in AIDS-associated Kaposi sarcoma. *Clin Cancer Res* 2020;26:558-565.

#### Etoposide

Hosseiniipour MC, Kang M, Krown SE, et al. As-needed vs immediate etoposide chemotherapy in combination with antiretroviral therapy for mild-to-moderate AIDS-associated Kaposi sarcoma in resource-limited settings: A5264/AMC-067 randomized clinical trial. *Clin Infect Dis* 2018;67:251-260.

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Cianfrocca M, Lee S, Von Roenn J, et al. Randomized trial of paclitaxel versus pegylated liposomal doxorubicin for advanced human immunodeficiency virus-associated Kaposi sarcoma: evidence of symptom palliation from chemotherapy. *Cancer* 2010;116:3969-3977.

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Welles L, Saville MW, Lietzau J, et al. Phase II trial with dose titration of paclitaxel for the therapy of human immunodeficiency virus-associated Kaposi's sarcoma. *J Clin Oncol* 1998;16:1112-1121.

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### ABBREVIATIONS

<b>ART</b>	<b>antiretroviral therapy</b>	<b>KICS</b>	<b>KSHV–associated inflammatory cytokine syndrome</b>
<b>BED</b>	<b>biologically effective dose</b>	<b>KS</b>	<b>Kaposi sarcoma</b>
<b>CBC</b>	<b>complete blood count</b>	<b>KSHV</b>	<b>Kaposi sarcoma-associated herpesvirus</b>
<b>CR</b>	<b>complete response</b>	<b>MCD</b>	<b>multicentric Castleman disease</b>
<b>DDIs</b>	<b>drug-drug interactions</b>	<b>NHL</b>	<b>non-Hodgkin lymphoma</b>
<b>EGD</b>	<b>esophagogastroduodenoscopy</b>	<b>NSAIDs</b>	<b>nonsteroidal anti-inflammatory drugs</b>
<b>GI</b>	<b>gastrointestinal</b>	<b>OI</b>	<b>opportunistic infection</b>
<b>HHV-8</b>	<b>human herpesvirus 8</b>	<b>PD</b>	<b>progressive disease</b>
<b>HIV</b>	<b>human immunodeficiency virus</b>	<b>PR</b>	<b>partial response</b>
<b>ICI</b>	<b>immune checkpoint inhibitor</b>	<b>PWH</b>	<b>people with HIV</b>
<b>ID</b>	<b>infectious disease</b>	<b>REMS</b>	<b>risk evaluation and mitigation</b>
<b>IHC</b>	<b>immunohistochemistry</b>	<b>SD</b>	<b>stable disease</b>
<b>IL</b>	<b>interleukin</b>	<b>SPEP</b>	<b>serum protein electrophoresis</b>
<b>IMRT</b>	<b>intensity-modulated radiation therapy</b>		
<b>IRIS</b>	<b>immune reconstitution inflammatory syndrome</b>		



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NCCN Categories of Evidence and Consensus	
<b>Category 1</b>	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
<b>Category 2A</b>	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
<b>Category 2B</b>	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
<b>Category 3</b>	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
<b>Preferred intervention</b>	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
<b>Other recommended intervention</b>	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
<b>Useful in certain circumstances</b>	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.



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### Discussion

This discussion corresponds to the NCCN Guidelines for Kaposi Sarcoma. Last updated: October 21, 2024

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## Kaposi Sarcoma

### Overview

Kaposi sarcoma is a multifocal malignancy of endothelial cells, which presents with characteristic purpuric, red or brown papules. Four types of Kaposi sarcoma have been described: HIV-associated, classic, iatrogenic or transplant-associated, and endemic.<sup>1-3</sup> Kaposi sarcoma is universally associated with Kaposi sarcoma-associated herpesvirus (KSHV) infection (also known as human herpesvirus-8, or HHV-8).<sup>2</sup> Serologic confirmation of KSHV infection is present in 95% to 98% of patients with Kaposi sarcoma.<sup>2,3</sup> KSHV infections are usually asymptomatic. Like other herpesviruses, KSHV establishes latent infection in humans that is life-long. Hence, persons with KSHV infection are at life-long risk of Kaposi sarcoma and other KSHV-associated diseases. Immunosuppression of various forms (ie, immunosenescence, HIV-associated and iatrogenic) is recognized to be an important factor in the pathogenesis of Kaposi sarcoma.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kaposi Sarcoma provide treatment recommendations for patients with HIV-associated, classic, iatrogenic, and endemic Kaposi sarcoma and are intended to assist health care providers with clinical decision-making. This Discussion section provides an overview of the literature supporting the recommendations included in the guidelines. The Panel also publishes separate NCCN Guidelines for Cancer in People with HIV (available at [www.NCCN.org](http://www.NCCN.org)), which give recommendations regarding human immunodeficiency virus (HIV) management during cancer therapy, drug-drug interactions (DDIs) with antiretrovirals and cancer therapies, radiation therapy, and supportive care for people with HIV (PWH). Recommendations for the management of Kaposi sarcoma for patients in sub-Saharan Africa can be found in the NCCN Harmonized Guidelines™ for Sub-Saharan Africa for Kaposi Sarcoma (available at [www.NCCN.org/harmonized](http://www.NCCN.org/harmonized)).

### Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website at [www.NCCN.org](http://www.NCCN.org).

### Literature Search Criteria

Prior to the update of the NCCN Guidelines® for Kaposi Sarcoma, an electronic search of the PubMed database was performed to obtain key literature in Kaposi Sarcoma published since the previous Guidelines update, using the search term: Kaposi Sarcoma. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.<sup>4</sup>

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the Panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

### Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.<sup>5</sup> NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing





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on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

### HIV-Associated Kaposi Sarcoma

Historically, when Kaposi sarcoma occurred in the setting of HIV seropositivity, it was considered an AIDS-defining illness and was referred to as AIDS-related or epidemic Kaposi sarcoma. The risk for Kaposi sarcoma in the setting of HIV was previously reported to be increased as much as 3640-fold over the general U.S. population,<sup>6-10</sup> but this risk has declined in the antiretroviral therapy (ART) era.<sup>6,11-14</sup> Still, estimates indicate that the risk of Kaposi sarcoma in PWH between 2009 and 2012 was elevated approximately 498-fold compared with the general U.S. population,<sup>11</sup> and Kaposi sarcoma accounts for approximately 12% of cancers diagnosed in PWH, with an estimated 765 to 910 cases diagnosed per year in the United States.<sup>15,16</sup> The 5-year survival of patients with AIDS-related Kaposi sarcoma has improved in the post-ART era, from 12.1% in 1980 to 1995 to as high as 88% in the post-ART era.<sup>17-</sup>

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When immunosuppression is advanced, HIV-associated Kaposi sarcoma is more common, more aggressive, and more likely to involve viscera, mucosa, and lymph nodes and cause lymphedema than when

immunosuppression is minimal. In fact, CD4+ T-cell counts and HIV viral load correlate with the risk of Kaposi sarcoma development in PWH, and effective ART lowers that risk.<sup>20</sup> Evidence also suggests that ART improves prognosis of Kaposi sarcoma in PWH. However, HIV-associated Kaposi sarcoma can also occur in PWH with normal CD4+ T-cell counts and undetectable HIV viral load. Similar to classic Kaposi sarcoma, these cases commonly occur with advanced age. Even with well-controlled HIV, studies have demonstrated more rapid immunosenescence than HIV-negative cohorts, which may permit Kaposi sarcoma to become clinically apparent in KSHV-seropositive individuals. Typically presenting with more limited disease than in PWH with advanced immunosuppression, these cases have prompted a shift toward favoring the term “HIV-associated Kaposi sarcoma” over “AIDS-related Kaposi sarcoma” in those with otherwise preserved immune function.

HIV management during treatment of Kaposi sarcoma in PWH is critical. Co-management by oncology and HIV specialists is recommended for the duration of therapy. Oncology and HIV specialists, along with both an oncology pharmacist and HIV pharmacist if available, should review proposed cancer therapy, supportive care medications, and ART for possible DDIs and overlapping toxicities prior to initiation of therapy for PWH. The NCCN Guidelines for Cancer in People with HIV (available at [www.NCCN.org](http://www.NCCN.org)) provide additional recommendations on HIV screening, linkage to HIV care, prevention of opportunistic infections, DDIs between antiretrovirals and cancer therapies, radiation therapy, and supportive care for PWH.

### Classic Kaposi Sarcoma

Classic Kaposi sarcoma generally involves indolent cutaneous lesions, often of the lower extremities, which may wax and wane or slowly progress over years to decades. It is most common in people of Mediterranean, Eastern European, Middle Eastern, and/or Jewish origins,



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with a mean age of 74 years at diagnosis.<sup>1,3</sup> It is reported to be 7 to 15 times more common in males than in females.<sup>1,3</sup> Synchronous primary malignancies may be fairly common in patients with classic Kaposi sarcoma, and are more likely to be the cause of death in these patients.<sup>3</sup>

### Iatrogenic Kaposi Sarcoma

When Kaposi sarcoma occurs in the context of immunosuppressive therapy (for organ transplant or other reasons), it is called iatrogenic or transplant-associated Kaposi sarcoma.<sup>1</sup> Lesions often appear 2 to 8 months after initiation of immunosuppression, and occur 2 to 3 times more often in males.<sup>1</sup> Although this form of Kaposi sarcoma can be aggressive and involve lymph nodes, mucosa, and/or visceral organs, it frequently responds to cessation of immunosuppression. When this is not feasible, reduction of immunosuppression or change to use of mTOR inhibitors as the immunosuppressive therapy can improve control of Kaposi sarcoma.<sup>21</sup>

### Endemic Kaposi Sarcoma

Endemic Kaposi sarcoma occurs in children and younger adults (<40 years of age) of equatorial Africa and may also occur in immigrants from the region. It is usually more aggressive than classic Kaposi sarcoma, sometimes with visceral, bone, and/or lymph node involvement, although it often begins as skin lesions that remain indolent for several years.<sup>1</sup> As with classic Kaposi sarcoma, endemic disease is 10 to 17 times more common in males than in females.<sup>1</sup>

## Management of Kaposi Sarcoma

### Diagnosis and Workup of Kaposi Sarcoma

Multiple clinical and histologic presentations of Kaposi sarcoma have been described. Mucosal and cutaneous lesions may be characterized clinically as papules, plaques, nodules (sometime pedunculated), and bullae. Large plaques may form from coalescence of smaller plaques or nodules and

may ulcerate or develop bullae. Hyperpigmented macules (lacking change in palpable skin thickness) rarely represent active disease; rather, they are very common after lesion regression due to residual hemosiderin-related pigmentation. Histologic subtypes include anaplastic, telangiectatic, lymphedematous, hyperkeratotic, keloidal, micronodular, pyogenic granuloma-like, ecchymotic, and intravascular variants of Kaposi sarcoma.

Lymphedema is a common complication of Kaposi sarcoma and may also be a predisposing factor to the development of Kaposi sarcoma. Lymphedema can be caused by not only nodal involvement but involvement of lymphatic vessels. Hyperkeratotic variants with verrucous and hyperkeratotic changes are notably associated with chronic and severe Kaposi sarcoma-associated lymphedema and may require deeper biopsy to confirm presence of Kaposi sarcoma.

As described in the guidelines above, Kaposi sarcoma is diagnosed by pathology and immunophenotyping. Workup should include a history and physical exam that includes any history of additional immunosuppression such as transplant or glucocorticoids (including topical, intranasal, inhaled, intraarticular, as well as systemic), complete blood count (CBC) with differential, comprehensive metabolic panel, and HIV screening and/or diagnostic testing. In addition, complete skin, oral, and lymph node exams, with documentation of edema and photography of oral, conjunctival, and cutaneous lesions for documentation of extent of disease are recommended. It is important to note that certain opportunistic infections can result in cutaneous lesions that can mimic Kaposi sarcoma lesions (eg, bacillary angiomatosis, blastomycosis, cryptococcosis).<sup>22-25</sup> Therefore, in addition to biopsy of suspected lesions, involvement of an HIV specialist to evaluate for coexisting opportunistic infections is appropriate in PWH and those with advanced immunosuppression.

For PWH, care coordination between the HIV specialist and the oncology team is recommended. *Recommendations for the management of cancer*



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in PWH are presented in the NCCN Guidelines for Cancer in People with HIV (available at [www.NCCN.org](http://www.NCCN.org)). All PWH should have recent T-cell subsets including quantitative CD4+ T-cell counts and HIV viral load to assess immune function and HIV control.

Depending on symptoms and findings that may be concerning for visceral or bone involvement, additional workup may be necessary. This may include fecal occult blood testing (FOBT), chest x-ray, chest/abdomen/pelvis CTs with contrast, MRI with and without contrast, upper endoscopy, or colonoscopy.

Unexplained fevers, particularly when associated with cytopenias occurring in the context of Kaposi sarcoma, should prompt workup of multicentric Castleman disease (MCD) and KSHV-associated inflammatory cytokine syndrome (KICS) with C-reactive protein, KSHV serum viral load, serum protein electrophoresis (SPEP), IL-6, and IL-10. KICS and MCD share clinical features and are only distinguished from each other by biopsy of lymphadenopathy or other structures demonstrating pathologic characteristics of MCD.<sup>26</sup> In the event of suspected coexisting KSHV-associated lymphoma, MCD, or KICS, additional workup including imaging may be necessary, such as fluorodeoxyglucose (FDG)-PET/CT scans and laboratory workup noted above.

It is important to note that interpretation of imaging in PWH who have cancer is complicated by the increased incidence of non-malignant lesions that may be mistaken for cancer spread or recurrence. Opportunistic infections in the lung include *Mycobacterium tuberculosis* (Mtb), cytomegalovirus (CMV), invasive fungal infections, and *Pneumocystis jirovecii* pneumonia (PCP).<sup>27</sup> Furthermore, non-infectious, non-malignant pulmonary manifestations of HIV can be difficult to interpret on imaging studies, including interstitial pneumonia and granulomatous disease.<sup>27,28</sup> Furthermore, brain lesions seen in PWH may result from opportunistic

infections, such as viral encephalitis, aspergillosis, toxoplasmosis, cryptococcosis, bacterial meningitis, tuberculosis, progressive multifocal leukoencephalopathy, and mycobacterium avium complex (MAC).<sup>29,30</sup> PWH are at increased risk of lymphomas including primary central nervous system lymphoma. Benign non-infectious brain lesions can also occur in PWH (eg, vascular complications, hydrocephalus).<sup>29,30</sup> Similarly, immune response to HIV and opportunistic infections commonly cause lymphadenopathy in PWH, which can be seen on CT and may be avid on F-18 FDG PET/CT.<sup>31,32</sup> Non-malignant causes of lymphadenopathy are more common in patients with higher HIV viral loads and lower CD4+ T-cell counts.<sup>33</sup> Therefore, involvement of an HIV specialist to assist with determining the need for a workup of suspected concurrent opportunistic infection or HIV-associated complications may be appropriate.

### Staging of Kaposi Sarcoma

As delineated in the guidelines above, Kaposi sarcoma is staged using a TIS system in which aspects of the tumor (T), immune system (I), and systemic disease (S) are assessed with a 0 for good risk and 1 for poor risk.<sup>34</sup> Data have shown that the I stage has less prognostic value than the T or S stages for PWH on ART.<sup>18</sup> Kaposi sarcoma staged as T1S1 appears to have the worst prognosis. In a study of 211 patients with AIDS-related Kaposi sarcoma, those staged as T1S1 had a 3-year survival rate of 53%, whereas for those staged as T0S0, T1S0, or T0S1, the 3-year survival rates were 88%, 80%, and 81%, respectively ( $P = .0001$ ).<sup>18</sup>

### Assessing Response of Kaposi Sarcoma

Response of Kaposi sarcoma to therapy has been formally defined by the AIDS Clinical Trials Group (ACTG) Oncology Committee as follows<sup>34</sup>:

- Complete response (CR) is defined as the absence of any detectable residual disease, including tumor-associated (local) edema, persisting for at least 4 weeks. Patients known to have had visceral disease should have restaging with appropriate





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endoscopic or radiographic procedures relevant to sites involved at baseline.

- Partial response (PR) is defined as no new mucocutaneous lesions, visceral sites of involvement, or the appearance or worsening of tumor-associated edema or effusions; AND
  - A  $\geq 50\%$  decrease in the number of all previously existing lesions lasting for at least 4 weeks; OR
  - Complete flattening of at least 50% of all previously raised lesions (ie, 50% of all previously nodular or plaque-like lesion become macules); OR
  - A 50% decrease in the sum of the products of the largest perpendicular diameters of at least five measurable lesions.
  - Note that when there is residual tumor-associated edema or effusion, but disease otherwise meets criteria for CR, response should be classified as partial.
- Stable disease (SD) is defined as any response that does not meet the criteria for progressive disease (PD) or PR.
- PD is defined as an increase of  $\geq 25\%$  in the size of pre-existing lesions and/or the appearance of new lesions or sites of disease and/or a change in the character of the skin or oral lesions from macular to plaque-like or nodular of  $\geq 25\%$ . If new or increasing tumor-associated edema or effusion develop, disease is considered progressive.

Many Kaposi sarcoma lesions that are responsive to therapy will flatten and change color but remain pigmented (ranging from very dark brown to tan) as non-palpable macular skin lesions. Biopsy of these will often confirm lack of residual tumor cells with residual siderophages and/or free hemosiderin pigment in the tissue. This is attributed to long-term iron deposition resulting from red blood cell extravasation into the tissue (dermal layer characteristically in cutaneous lesions). Care should be taken to distinguish this “tattoo” effect from active disease, as additional

therapy is not indicated for the former. Over time, many lesions will gradually fade, depending on many factors, including chronicity and size of the lesion as well as degree to which red blood cell extravasation occurred.

### Initial Management of Kaposi Sarcoma

#### *Optimizing Immune Function*

For all types and severities of Kaposi sarcoma, optimizing immune function is a critical component of management, and in some cases may be the only intervention needed for initial control. Iatrogenic immunosuppression—including over-the-counter topical or intranasal glucocorticoids—is often identified on a careful medication history in persons with and without HIV prior to initial presentation or flare of Kaposi sarcoma. Patients and their providers should be educated on the importance of cessation and avoidance of immunosuppressive therapies whenever possible, including topical, local, and systemic therapies. Otherwise, immunosuppressive therapy should be minimized as much as possible to reduce risk of Kaposi sarcoma progression and flares. PWH additionally benefit from maximizing HIV suppression and immune reconstitution with appropriate ART.

#### *Limited Cutaneous Kaposi Sarcoma*

PWH with limited cutaneous disease that is asymptomatic and cosmetically acceptable to the patient may be treated with ART alone (see below). Persons without HIV can be observed until the disease becomes symptomatic and/or cosmetically bothersome or progressive.

PWH with symptomatic and/or cosmetically bothersome limited cutaneous disease should be treated with ART and with the most minimally invasive and least toxic therapy possible. When necessary, a limited number of cycles of systemic therapy (eg, 3–6; options discussed below) may be sufficient for those initiating or re-initiating ART. Other options include



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radiation, and for small lesions (ie,  $\leq 1$  cm), topical treatment, intralesional chemotherapy, cryotherapy, and local excision (all discussed below). Intralesional chemotherapy and radiation to plantar and palmar surfaces may be useful in selected cases but should be approached with caution because of toxicity or functional adverse events. Increased risk of long-term wound healing, particularly in the setting of coexisting lymphedema, is a concern.

The same treatment options, without ART, are recommended for patients without HIV who have limited cutaneous disease that is symptomatic and/or cosmetically bothersome.

If disease progresses on therapy in PWH, consider biopsy of lesions since they may be areas of post-inflammatory pigment and/or mimickers of Kaposi sarcoma. If it is Kaposi sarcoma, the individual should be evaluated for inadequate HIV control or other immunosuppressant use, which could be contributing factors to inadequate Kaposi sarcoma control. Change in ART in conjunction with an HIV specialist may be warranted for some cases (see the NCCN Guidelines for Cancer in People with HIV, available at [www.NCCN.org](http://www.NCCN.org)).

For PWH with adequate HIV control and those without HIV, treatment options should be determined by the extent of disease. If disease is stable or a response is seen on initial therapy, the patient should be observed (while ART is continued in PWH). If the disease progresses or relapses after an initial response to therapy, repeat use of the previously effective therapy may be considered, particularly if response was durable and the therapy was well tolerated.

Preferred initial treatment for patients with advanced cutaneous, oral, visceral, or nodal Kaposi sarcoma is systemic therapy, in conjunction with ART for PWH. For those not eligible for systemic therapy, radiation can be used, in conjunction with ART for PWH. The data supporting these

treatment options are described below. Well-designed clinical trials may also be considered for frontline therapy, with the consideration that established systemic therapies are often most appropriate for frontline therapy of *symptomatic* visceral disease.

It is important to note that individual Kaposi sarcoma lesions may be distinct clones that arise because of the common risk factors of immunosuppression and latent KSHV infection as opposed to metastases. Furthermore, persistence of KSHV infection results in ongoing risk of recurrence/disease progression. Currently, eradication of KSHV is not possible. Therefore, treatment of existing disease may not prevent occurrence of future lesions. Given this and the fact that many presentations of Kaposi sarcoma are not life-threatening, the goals of therapy are focused on disease control. Wide excisions with the goal of achieving negative margins are not indicated, as they do not contribute to control of Kaposi sarcoma. Local excisions should instead be used for limited symptomatic lesions where systemic therapy is not appropriate. When such excisions are likely to be complex, other local therapies including cryotherapy or radiation can be favorable alternatives. Systemic therapy with risk of long-term toxicities should be reserved for more serious presentations.

### **Antiretroviral Therapy for People with HIV**

Reconstitution of immune function, maintenance of viral suppression, and avoidance of additional immunosuppression are critical to prevent additional Kaposi sarcoma lesions and maintain response to therapy in PWH. In fact, in the setting of limited cutaneous disease, remissions or SD may occur with optimization of immune function and HIV viral suppression alone.<sup>35-41</sup> Therefore, co-management with an HIV specialist to optimize suppression of HIV and reconstitution of immune function with ART is important for patients with AIDS-related Kaposi sarcoma (see the NCCN Guidelines for People with HIV, available at [www.NCCN.org](http://www.NCCN.org)).





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### ***Immune Reconstitution Inflammatory Syndrome***

Initiation of ART may result in immune reconstitution inflammatory syndrome (IRIS) within 3 to 6 months in a reported 6% to 39% of patients with AIDS-related Kaposi sarcoma.<sup>42-46</sup> Kaposi sarcoma-associated IRIS (KS-IRIS) is characterized by first presentation or paradoxical worsening of pre-existing Kaposi sarcoma infection following ART initiation.<sup>47</sup> Clinical manifestations of IRIS may be challenging to distinguish from natural history of PD and may include the development of new lesions or enlargement of existing lesions, worsening lymphadenopathy, increased tenderness, and lymphedema. Individuals with pulmonary involvement, concurrent or recent use of glucocorticoids, and/or advanced immunosuppression may be at increased risk.<sup>42,43,45</sup> The risk of IRIS is higher in patients with baseline low CD4 T-cell counts and high HIV viral loads.<sup>48</sup> In contrast with management of IRIS for some opportunistic infections, glucocorticoids are generally contraindicated in Kaposi sarcoma, as well as in Kaposi sarcoma-associated IRIS, because of the potential for life-threatening Kaposi sarcoma exacerbation resulting from stimulatory effects of glucocorticoids on Kaposi sarcoma spindle cells and association of glucocorticoid use with increased mortality.<sup>43,49,50</sup> KS-IRIS is an indication for urgent initiation of systemic Kaposi sarcoma therapy and should involve coordination with an HIV specialist. Signs of past IRIS may be an indication for earlier initiation of systemic Kaposi sarcoma therapy. ART should not be delayed or discontinued unless life-threatening IRIS develops.

PWH with advanced Kaposi sarcoma not on ART at the time of presentation should start systemic therapy as soon as possible after the initiation of ART to minimize the risk of severe KS-IRIS. A randomized open-label clinical trial compared two treatment strategies in patients with mild-to-moderate AIDS-related Kaposi sarcoma in sub-Saharan Africa: ART with concurrent low-dose oral etoposide versus ART with etoposide later, as needed.<sup>51</sup> Results demonstrated that early initiation of

chemotherapy and ART together decreased early progression of Kaposi sarcoma and IRIS. Early progression of Kaposi sarcoma and IRIS incidences with immediate etoposide versus ART alone were 16% versus 39%, and 7% versus 21%, respectively. Another clinical trial compared immediate versus as-needed oral etoposide in PWH with mild-to-moderate Kaposi sarcoma initiating ART.<sup>52</sup> Immediate oral etoposide delayed Kaposi sarcoma progression ( $P = .021$ ), decreased suspected KS-IRIS events ( $P = .003$ ), and decreased time to initial Kaposi sarcoma response ( $P = .003$ ). However, no long-term clinical benefit was observed compared to the as-needed approach.

Whereas there are no prospective trials using thalidomide for Kaposi sarcoma-associated IRIS, successful control of steroid-refractory IRIS with thalidomide has been reported, and the immunomodulatory drugs (IMiDs), including thalidomide, are an active class of therapy in Kaposi sarcoma.<sup>53-</sup>

<sup>56</sup>

### ***Topical Therapies***

Topical therapies are an option for patients with limited cutaneous disease that is symptomatic and/or cosmetically bothersome. Alitretinoin gel, a retinoid, was studied in a phase III vehicle-controlled, double-blind, multi-centered study, in which 134 patients with AIDS-related Kaposi sarcoma received either 0.1% alitretinoin gel or vehicle gel twice daily for 12 weeks.<sup>57</sup> The cutaneous tumor response rates were 37% in the alitretinoin group compared with 7% in the control group. Another very similar randomized, multicenter, double-blind, vehicle-controlled study also compared tumor response rates in patients with AIDS-related Kaposi sarcoma between an alitretinoin group and a control group.<sup>58</sup> Response rates in the 268 patients were 35% for those who received 0.1% alitretinoin gel compared with 18% for those who received the vehicle gel. In both of these studies, alitretinoin gel was well tolerated, with mostly mild to moderate adverse events that were limited to the application site and



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that were relieved when treatment was stopped. Data on the use of alitretinoin in classic Kaposi sarcoma is limited to two case reports, in which one patient showed significant improvement and the other did not.<sup>59,60</sup>

Imiquimod is a topical immune response modulator with antiviral and antitumor activity.<sup>61</sup> It is used in a variety of skin conditions including malignancies and warts.<sup>61,62</sup> Case reports have shown that imiquimod cream can be safe and effective in some patients with classic or transplant-associated Kaposi sarcoma.<sup>63-70</sup> In a single-center, open-label, phase I/II trial, 17 patients without HIV who had Kaposi sarcoma received imiquimod 5% cream 3 times per week for 24 weeks.<sup>71</sup> The response rate was 47%. Over half of the patients reported local itching and erythema, but treatment was generally well tolerated. Imiquimod is not well studied as a treatment for patients with cutaneous AIDS-related Kaposi sarcoma.<sup>72,73</sup> The Panel includes imiquimod as an option for patients with limited cutaneous AIDS-related Kaposi sarcoma based on extrapolation from the data presented above in other settings, expert opinion, and non-published anecdotal data.

### ***Intralesional Chemotherapy***

Intralesional vinblastine is another option for patients with limited mucocutaneous disease that is symptomatic and/or cosmetically bothersome. Intralesional injection of vinblastine has been studied in case reports, case series, and one small randomized trial of patients with oral AIDS-related Kaposi sarcoma.<sup>74-80</sup> In a large series of 144 oral Kaposi sarcoma lesions in 50 PWH, CR was seen in 74% of lesions and PR in 26%.<sup>77</sup> The recurrence rate was 26%, with a mean disease-free period of 12.9 weeks. Consistent with the safety profile seen in other studies, pain was reported by 72% of participants, ulceration occurred in 22%, and temporary numbness was seen in 12%. Pain is generally mild to moderate and relieved with pain medication, and ulceration is generally self-limiting.

Studies on the use of intralesional vinblastine injection for cutaneous lesions are more limited.<sup>81,82</sup> In a trial of 11 patients with AIDS-related Kaposi sarcoma, 88% of cutaneous lesions showed a complete or partial clinical response.<sup>81</sup> Treatment resulted in inflammation and blistering of the lesion prior to healing, and the final results were not cosmetically optimal because of post-inflammation hyperpigmentation. Most patients reported aching pain 6 to 48 hours post-treatment that was relieved with pain medication.

Intralesional vinblastine has also been used in cutaneous lesions in patients with classic Kaposi sarcoma.<sup>83</sup>

### ***Local Excision***

Local excision is an option for patients with limited cutaneous disease that is symptomatic and/or cosmetically bothersome. Data regarding outcomes of the excision of cutaneous Kaposi sarcoma lesions are limited and appear to be restricted to individuals without HIV.<sup>84-88</sup> Wide excisions with goal of negative margins is not indicated as this does not contribute to prevention of additional Kaposi sarcoma lesion development as discussed above.

### ***Radiation Therapy***

Kaposi sarcoma is radioresponsive, with CR rates of treated lesions reported in the range of 60% to 93%.<sup>69,89-93</sup> Radiation therapy for Kaposi sarcoma is used in patients with limited cutaneous disease that is symptomatic and/or cosmetically bothersome. For patients with advanced disease, systemic therapy is preferred over radiation therapy in first-line and for relapsed/refractory disease as long as systemic therapy is feasible based on performance status and comorbidities. Radiation in this setting should be reserved for circumstances when systemic therapy is not feasible or when palliative therapy is needed to mitigate pain or other symptoms.<sup>94</sup>



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When radiation is used, hypofractionated regimens (eg, 20 Gy in 5 fractions) appear to be equally effective as the standard regimen of 24 Gy in 12 fractions.<sup>95,96</sup> Dose fractionation should be based on the site of treatment with consideration for surrounding normal tissue tolerance. Lower doses are preferred for smaller and more superficial lesions. Higher doses may be preferred for more extensive, deeply invasive lesions. More fractionated regimens may be preferred for sites with adjacent radiosensitive structures, such as the oral cavity.

The side effects of radiation for Kaposi sarcoma are site-dependent, but typically manageable given the low doses needed to achieve a response.<sup>89-92</sup> Still, the risk of secondary cancer, severe or worsening lymphedema, and long-term wound healing complications may be increased after radiation. Early recognition and treatment of dermatitis, oral mucositis, and lymphedema are especially important.<sup>89,91,97</sup> The risk of lymphedema is already elevated in patients with Kaposi sarcoma and may increase after radiation.<sup>98</sup> Therefore, caution should be exercised with the use of radiation to sites of pre-existing lymphedema. Early referral to and co-management with a lymphedema specialist is recommended. In the setting of advanced cutaneous disease, radiation therapy should be reserved for cases where systemic therapy is not feasible, with the goal of palliation or short-term disease management until systemic therapy may be delivered. Radiation therapy may also be used for disease refractory to multiple types of systemic therapy.

### **Cryotherapy**

Cryotherapy is also an option for patients with limited cutaneous disease that is symptomatic and/or cosmetically bothersome. In a small study of 30 patients, 125 lesions were treated with cryotherapy.<sup>99</sup> Nineteen (63%) patients experienced a CR without recurrence. Blistering was frequent, local pain was limited, and the treatment was well tolerated overall. Other

studies also suggest that cryotherapy can be effective in patients with classic Kaposi sarcoma.<sup>70</sup>

### **Systemic Therapy**

The preferred first-line systemic therapy is liposomal doxorubicin. In a randomized phase III trial, 258 patients with advanced AIDS-related Kaposi sarcoma were randomized to receive pegylated-liposomal doxorubicin or doxorubicin, bleomycin, and vincristine (ABV).<sup>100</sup> The overall response rate was 46% (95% CI, 37%–54%) in the liposomal doxorubicin arm and 25% (95% CI, 17%–32%) in the ABV arm. The median time to treatment failure was approximately 4 months in both groups. Most patients in both arms experienced  $\geq 1$  grade 3–4 adverse event, with leukopenia, nausea/vomiting, anemia, and peripheral neuropathy as the most common adverse events in the liposomal doxorubicin group. Pegylated-liposomal doxorubicin was also compared with bleomycin and vincristine (BV) in another randomized trial of patients with AIDS-related Kaposi sarcoma ( $n = 241$ ).<sup>101</sup> As in the other trial, response rates were superior in the liposomal doxorubicin group compared with the BV group (59% vs. 23%;  $P < .001$ ). Pegylated-liposomal doxorubicin resulted in an increased risk of neutropenia but was less likely to result in early treatment cessation. Liposomal doxorubicin has also been shown to have activity in classic and transplant-associated Kaposi sarcoma.<sup>69,102</sup>

Liposomal doxorubicin is associated with risk of cardiotoxicity.<sup>103-105</sup> Therefore, an echocardiogram should be performed prior to initial course of liposomal doxorubicin and should be repeated as clinically indicated.<sup>106</sup> Consider limiting lifetime dose per prescribing guidelines; however, some data suggest that the patients who need continued treatment may be safely treated beyond 1000 mg/m<sup>2</sup>.<sup>107</sup>

An alternative option for first-line systemic therapy for limited cutaneous and advanced disease is paclitaxel. Early studies showed that it has





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significant activity in the advanced disease setting, with neutropenia as the most frequent dose-limiting toxicity.<sup>69,108-110</sup>

One trial randomized 73 patients with advanced AIDS-related Kaposi sarcoma to paclitaxel or pegylated-liposomal doxorubicin.<sup>111</sup> The two arms were statistically equivalent with regard to response rates (56% for paclitaxel vs. 46% for pegylated-liposomal doxorubicin;  $P = 0.49$ ), median progression-free survival (17.5 vs. 12.2 months;  $P = 0.66$ ), and 2-year survival (79% vs. 78%;  $P = 0.75$ ). A trend toward increases in grade 3 to grade 5 toxicity was seen in the paclitaxel arm (84% vs. 66%;  $P = .077$ ), with 1 lethal, grade 5 pulmonary embolism in a patient treated with paclitaxel. A systematic review of randomized trials and observational studies in patients with advanced AIDS-related Kaposi sarcoma found no evident differences between liposomal doxorubicin, liposomal daunorubicin, and paclitaxel, although the number of studies identified was low.<sup>112</sup> Data on the use of paclitaxel in non-AIDS-related Kaposi sarcoma are more limited.<sup>113,114</sup>

### Surveillance of Patients with Kaposi Sarcoma

Patients treated for Kaposi sarcoma who do not require active treatment and who are without signs of progression should be followed periodically based on degree of response to therapy and, if applicable, degree of HIV viremia and immune reconstitution. Surveillance should include history and physical (including complete skin and oral exams and documentation of edema and history of additional immunosuppression such as transplant/glucocorticoids), CBC with differential, and comprehensive metabolic panel. For PWH, surveillance should also include T-cell subsets (CD4+ T-cell count) and HIV viral load, and ART adherence should be assessed.

If a change in disease is noted, lesions should be photographed for documentation. If there are signs and symptoms concerning for visceral

involvement, progression/refractory disease meriting new therapy, or a notable change in disease burden, various tests and imaging studies are indicated based on clinical circumstances. Testing for opportunistic infections should be conducted if signs of infection or inflammation are present. For patients with advanced cutaneous, oral, visceral, or nodal involvement, FOBT and chest x-ray are recommended. In patients with GI symptoms such as nausea, vomiting, diarrhea, abdominal pain, and melena/blood in stool, esophagogastroduodenoscopy, colonoscopy, and CT imaging should be performed. When pulmonary symptoms such as dyspnea and cough are present, bronchoscopy and chest CT should be performed.

It is important to note that KSHV is not eradicated with treatment of Kaposi sarcoma, and the risk of future Kaposi sarcoma persists even after complete remission. Avoidance of iatrogenic immunosuppression as well as optimization and monitoring of immune function and HIV control are important to minimize this risk because disease risk generally decreases with immune reconstitution. However, Kaposi sarcoma can persist, relapse, or present even in the setting of “normal” CD-4 counts. Less frequent (every 6–12 months) oncologic monitoring may be appropriate for select patients with Kaposi sarcoma that is limited in extent, stable for  $\geq 2$  years, and without ongoing immunosuppressive therapy and, for PWH, undetectable HIV viral loads, normal T-cell subsets, and regular follow-up with an HIV specialist.

### Systemic Therapy of Relapsed/Refractory Disease

At first progression, the same systemic therapy options as in first line (liposomal doxorubicin and paclitaxel, discussed above) may be considered as follows:

- If first-line therapy was tolerated and a durable response ( $>3$  months) was seen, then a repeat of the therapy used in first line should be considered.



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- If there was no response to first-line systemic therapy, then an alternative first-line therapy option should be given.

Following subsequent progressions, liposomal doxorubicin or paclitaxel, whichever has not yet been administered, is recommended.<sup>115,116</sup>

Following treatment with liposomal doxorubicin and paclitaxel, the Panel recommends pomalidomide as the preferred regimen. Pomalidomide was studied in a phase I/II trial of seven people without HIV and 15 PWH who had Kaposi sarcoma.<sup>55</sup> PWH were required to have viremia controlled and either progressive or stable Kaposi sarcoma on ART. Most of the participants (17 of 22; 77%) had previous therapy for Kaposi sarcoma, exclusive of ART.<sup>117</sup> The response rate was 60% in the PWH group (95% CI, 32%–84%). Grade 3–4 adverse events that might have occurred due to pomalidomide were neutropenia, infection, and edema. Pomalidomide has received accelerated U.S. Food and Drug Administration (FDA) approval for the treatment of adult patients with AIDS-related Kaposi sarcoma after failure of highly active ART and for patients without HIV who have Kaposi sarcoma.

Other treatment options for subsequent lines of therapy for relapsed/refractory disease include bortezomib, gemcitabine, lenalidomide, and vinorelbine. Etoposide, imatinib, ipilimumab + nivolumab (for classic Kaposi sarcoma), albumin-bound paclitaxel (if paclitaxel intolerant), pembrolizumab (for endemic and classic Kaposi sarcoma), sirolimus (for transplant Kaposi sarcoma), and thalidomide (for patients with IRIS) may also be useful under certain circumstances. Patients can continue through all treatment options listed, and treatments can be repeated if they were tolerated and the response was durable (≥3 months). In select cases, best supportive care may be an appropriate option.

Immune checkpoint inhibitors should not be used in patients with MCD or KICS because they can exacerbate these conditions. In a phase I study

assessing the safety of pembrolizumab in PWH and advanced cancer, a heavily pretreated patient with Kaposi sarcoma and prior history of KICS and elevated peripheral blood mononuclear cell-associated KSHV developed marked KSHV viremia and inflammation, leading to death.<sup>118</sup>

Bortezomib was studied in the dose-escalation, pilot AMC-063 trial, which included 17 patients with relapsed/refractory AIDS-related Kaposi sarcoma on ART.<sup>119</sup> The maximum tolerated dose was not reached. The PR rate was 60% in 15 evaluable patients and 83% in the 1.6 mg/m<sup>2</sup> cohort. The rest of the participants experienced SD. The most common adverse events were diarrhea, fatigue, and nausea.

Evidence for the use of gemcitabine in patients with refractory AIDS-related Kaposi sarcoma comes only from a retrospective analysis of 23 patients who had been treated with first-line ABV.<sup>120</sup> CR was seen in three patients (13%), PR in eight (35%), and SD in 11 (48%). Only one patient had PD. Grade 3–4 adverse events include leukopenia, pain, fatigue, and neutropenia. Gemcitabine has also been studied as first-line systemic therapy in a phase IIA trial in West Kenya, with a CR rate of 33% and a PR rate of 53%.<sup>121</sup> Gemcitabine also has activity in classic Kaposi sarcoma.<sup>69</sup>

The phase II AIDS Malignancy Consortium trial of lenalidomide evaluated response rates of relapsed/refractory Kaposi sarcoma in 42 persons with HIV.<sup>56</sup> PRs occurred in 60% of participants and treatment. The most common adverse events were neutropenia, fatigue, leukopenia, and diarrhea. The phase II ANRS 154 Lenakap trial evaluated the rate of PR or CR at week 24 after treatment with lenalidomide in 12 patients with relapsed/refractory AIDS-related Kaposi sarcoma.<sup>54</sup> The primary endpoint was the rate of PR or CR by Physical Global Assessment (PGA) criteria. Although none of the 10 patients who were evaluable at 24 weeks met PGA at 24 or 48 weeks, four met ACTG criteria for PR at 48 weeks.



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Evidence for the activity of vinorelbine in AIDS-related Kaposi sarcoma comes from a phase II trial of 35 assessable patients with PD.<sup>122</sup> Complete clinical responses were seen in 9%, and PRs were seen in 34%. The median duration of response was about 6 months. Neutropenia was the most frequent dose-limiting toxicity, but other side effects were mild and reversible, and the treatment was generally well tolerated. Data on the use of vinorelbine in classic and post-transplant Kaposi sarcoma are limited.<sup>123,124</sup>

Etoposide has been studied in multiple phase II trials and in the A5264/AMC-067 trial of patients with AIDS-related Kaposi sarcoma.<sup>52,125-127</sup> In one of the phase II trials, 36 patients with previously treated AIDS-related Kaposi sarcoma received a course of oral etoposide, and the overall response rate was 36%, with SD occurring in 33% of the participants.<sup>127</sup> The median duration of response was about 6 months. Grade 3–4 neutropenia occurred in 28%, and opportunistic infections occurred in 22%. The other phase II trials also showed oral etoposide to have clinical activity and be well tolerated. In the A5264/AMC-067 trial, 190 patients with mild-to-moderate AIDS-related Kaposi sarcoma in Africa and South America were randomized to ART alone with etoposide given for progression or ART plus immediate etoposide.<sup>52</sup> No difference in response between the groups was seen at 48 months. If oral etoposide is used, the Panel recommends the dose escalation used in this trial, as indicated in the guidelines. Etoposide also has activity in classic Kaposi sarcoma.<sup>69,128</sup>

Imatinib has activity in AIDS-related Kaposi sarcoma.<sup>129,130</sup> The strongest evidence comes from a multicenter phase II trial in which 30 patients were treated with imatinib.<sup>131</sup> Eighteen patients (60%) had received prior therapy. Partial response occurred in 33% and 20% had stable disease. The median duration of response was approximately 8 months, with disease progression in seven patients (23%). Grade 3–4 adverse events

attributed to imatinib included allergic reaction/hypersensitivity, nausea, dehydration, and cellulitis, but only five patients (17%) discontinued therapy because of adverse events.

Evidence for the use of ipilimumab + nivolumab for classical Kaposi sarcoma is limited to a phase II single-arm study in 18 patients with progressive disease after one or more lines of systemic therapy.<sup>132</sup> The primary endpoint of overall response rate was 87%. The secondary endpoint of 6-month progression-free survival rate was 76.5%. Grade 3–4 adverse events were experienced by four patients (one patient with grade 3 colitis, two patients with grade 3–4 lipase elevation, and one with grade 3 pneumonitis). Two patients discontinued treatment due to adverse events possibly related to treatment.

Evidence for the use of albumin-bound paclitaxel in Kaposi sarcoma appears to be limited to one abstract of a phase II trial of 6 patients with classic Kaposi sarcoma.<sup>133</sup> Partial (n = 2) or complete responses (n = 4) were seen in all patients. Grade 3 adverse events were neutropenia in half of the patients and thrombocytopenia in 1 of 6 patients.

A multicenter, phase II, single-arm trial treated 17 patients (8 with classic Kaposi sarcoma and 9 with endemic Kaposi sarcoma) with pembrolizumab.<sup>134</sup> The primary endpoint was the best overall response rate within a 6-month timeframe, and three or more responses among the 17 patients were needed for the primary endpoint to be met. Two patients (22%) had a CR, 10 patients had a PR (59%), and 5 patients (29%) had SD, with a best overall response rate of 71% (95% CI, 44–90), meeting the primary outcome. Adverse events occurred in 13 patients, including two grade 3 adverse events (1 acute cardiac decompensation and 1 granulomatous reaction).

For Kaposi sarcoma associated with immunosuppression from solid organ transplant, switching to sirolimus for immunosuppression may be sufficient





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for Kaposi sarcoma control and treatment. In a study of 15 patients who underwent kidney transplants and developed Kaposi sarcoma, cyclosporine therapy was stopped and sirolimus was initiated.<sup>21</sup> At 3 months after the start of sirolimus therapy, all cutaneous lesions had disappeared in all patients, all with confirmed histologic remission at 6 months. No acute episodes of rejection or changes in kidney-graft function were seen.

Thalidomide has been studied in AIDS-related Kaposi sarcoma in two phase II trials.<sup>135,136</sup> One of these trials included 17 assessable patients with PD.<sup>135</sup> PRs were seen in 47%, and SD was seen in 12%. Time to progression was a median 7.3 months. The most frequently reported side effects were drowsiness in 45% of participants and depression in 35%. Although no prospective trials have used thalidomide for Kaposi sarcoma-associated IRIS, successful control of steroid-refractory IRIS with thalidomide has been reported, and thalidomide is an active agent in Kaposi sarcoma.<sup>53</sup> The Panel thus believes that thalidomide may be a useful option for patients with Kaposi sarcoma and corticosteroid-refractory IRIS.

### Summary

Management of Kaposi sarcoma depends on location and extent of disease. PWH with limited cutaneous disease that is asymptomatic and cosmetically acceptable to the patient may be treated with ART alone. Remissions or SD may occur with optimization of immune function and HIV viral suppression alone.

Those with symptomatic and/or cosmetically bothersome limited cutaneous disease should be treated with therapy that is minimally invasive with the least toxicity possible, and with ART, if HIV-positive. Options include a limited number of cycles of systemic therapy, topical

treatment, intralesional chemotherapy, radiation, cryotherapy, and local excision.

Preferred initial treatment for patients with significant lymphedema and advanced cutaneous, oral, visceral, or nodal AIDS-related Kaposi sarcoma is ART with systemic therapy or systemic therapy alone for those without HIV. Alternatively, a well-designed clinical trial of an agent previously demonstrated to have activity is an appropriate option. For those not eligible for systemic therapy, radiation can be used (with ART for PWH). As lymphedema often complicates Kaposi sarcoma, early involvement of a lymphedema specialist is recommended.

Surveillance of patients treated for Kaposi sarcoma is important, as disease can recur after an initial CR and in the setting of normal values of T-cell subsets. Persistence of KSHV and emergence of distinct tumor clones can lead to disease progression and relapse. Furthermore, because individual Kaposi sarcoma lesions are often distinct clones as opposed to metastases, treatment of existing disease does not prevent occurrence of new lesions.

For relapsed/refractory disease, a typical systemic therapy sequence would be first-line liposomal doxorubicin, followed by second-line paclitaxel, followed by pomalidomide in the third line of treatment. Additional lines of other therapies can be given, and any systemic therapy that was tolerated with a durable response can be repeated.

Immunosuppression in general and glucocorticoids in any formulation should be avoided in patients with active or prior Kaposi sarcoma, or other KSHV-associated conditions, given the potential to cause significant flares or relapses of Kaposi sarcoma. The use of glucocorticoids should be limited to serious or life-threatening conditions for which these therapies are otherwise indicated (ie, anaphylaxis). Proceed with caution if using glucocorticoids and consult an HIV or Kaposi sarcoma specialist. Other



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therapies associated with flares of Kaposi sarcoma include those suppressing B- and T-cell numbers and/or function such as rituximab and cyclosporine, respectively.<sup>137,138</sup> Of note, patients with AIDS-related lymphomas who have concurrent Kaposi sarcoma are often able to receive multiagent chemotherapy regimens including glucocorticoids and rituximab without significant flare of Kaposi sarcoma if the regimen also includes agents active against Kaposi sarcoma such as anthracyclines. Careful monitoring of Kaposi sarcoma should be performed during and following conclusion of lymphoma therapy; additional Kaposi sarcoma-directed therapy may be required after completion of lymphoma regimens associated with prolonged immunosuppression (ie, rituximab, nucleoside analogues).

Overall, the survival of patients with Kaposi sarcoma has greatly improved, and long-term survival can be the goal for many patients. The goals of therapy for patients with advanced disease are namely reducing or reversing symptoms and mitigating end-organ damage. Complete remissions in this setting are rare, but effective therapy can result in long-term disease control.





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