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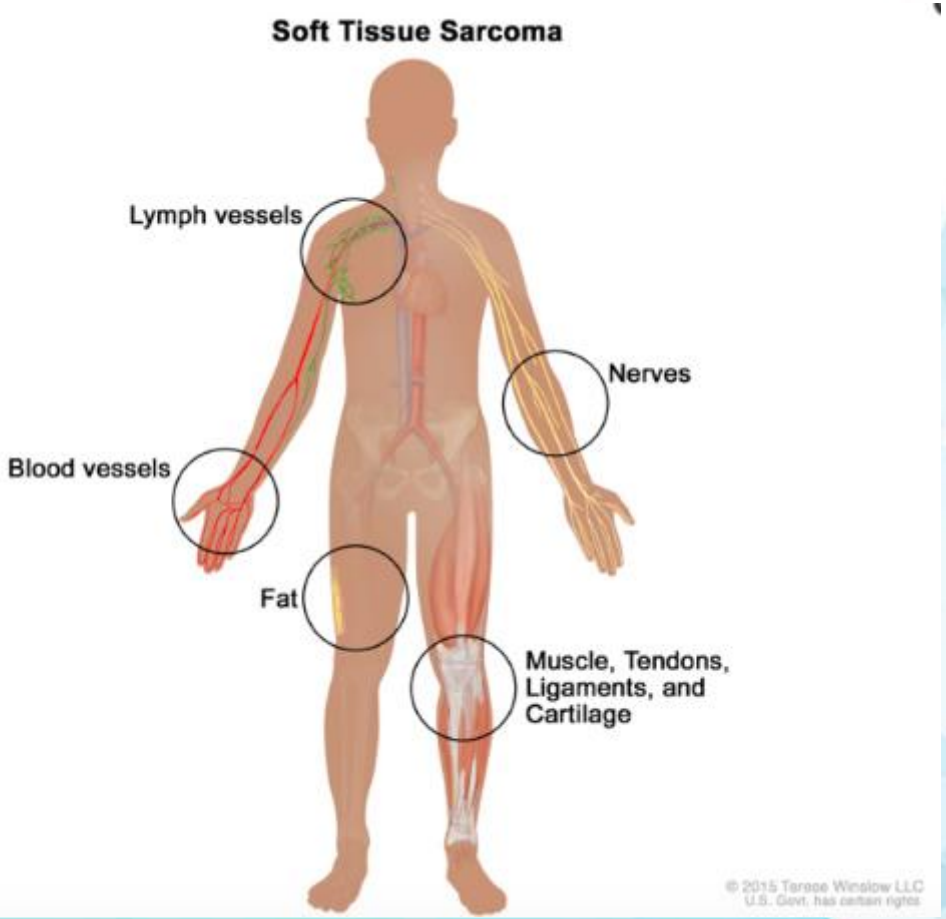
Flewship of IMRT&VMAT

Soft Tissue Sarcoma

- **Soft tissue sarcomas (STS)** are a heterogeneous group of rare tumors that arise from **mesenchymal cells** at all body sites.
- The malignant precursor cell(s) can differentiate along one or several lineages, such as muscle, adipose, fibrous, cartilage, nerve, or vascular tissue.
- These tumors arise most often in the **limbs** (**particularly the lower extremity**), followed in order of frequency by the abdominal cavity/retroperitoneum, the trunk/thoracic region, and the head and neck.



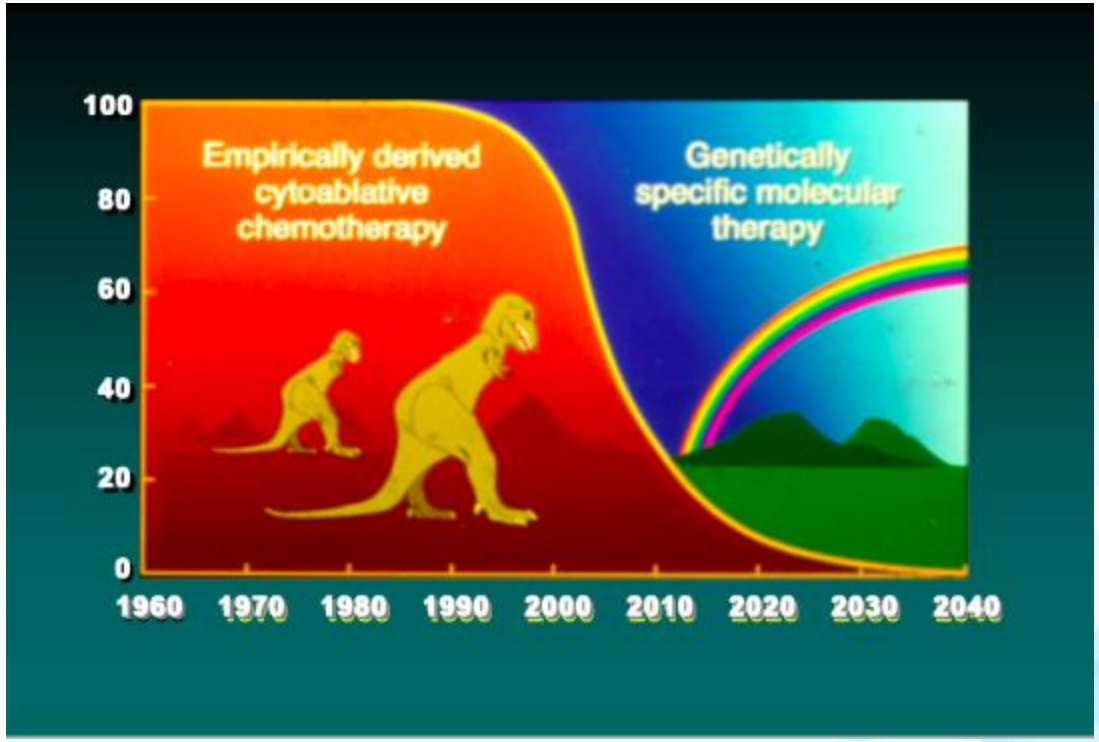
Soft Tissue Sarcoma

- INTRODUCTION

- Tumors arising in the soft tissue form a diverse and complex group, as they may display varying degrees of mesenchymal differentiation.
- Soft tissue **sarcomas account for <1% of the overall human burden of malignant tumors** but remain life threatening, and **approximately 40% of patients** with newly diagnosed soft tissue sarcoma die of the disease, corresponding to approximately 4,000 deaths each year in the United States.
- Soft tissue sarcoma, diagnosed at an **early stage**, is eminently **curable**. When diagnosed at the time of **extensive local** or **metastatic** disease, it is **rarely curable**. The relatively small number of cases and the great diversity in histopathologic features, anatomic sites, and biologic behaviors have made comprehensive understanding of these disease entities difficult. A better understanding is urgently needed to accelerate the development of new treatments.

Soft Tissue Sarcoma

- There are more than **50 histologic subtypes of STS**, many of which are associated with distinctive clinical profiles, responses to individual therapies, and prognoses.
- Even within a single histologic subtype, a heterogenous array of translocations or other molecular changes may be observed.
- While in the past these tumors were **all "lumped" together** and treated similarly, consensus is emerging that selection of treatment should be **histology driven**, **particularly in the setting of advanced disease.**



Soft Tissue Sarcoma (DIAGNOSIS AND STAGING)

- The presence of soft tissue sarcoma almost invariably is suggested by the development of a mass.
- This mass is usually large, is often painless, and may be associated by the patient with an episode of injury.
- Approximately one-third present with a size <5 cm, one third with a size 5 to 10 cm, and one-third with a size >10 cm.
- The focus of the clinical evaluation is to determine the likelihood of a benign or malignant soft tissue tumor, the involvement of muscular or neurovascular structures, and the ease with which biopsy or subsequent excision can be performed.
- **Definitive diagnosis** depends on biopsy results and histologic confirmation.

Soft Tissue Sarcoma (DIAGNOSIS AND STAGING)

- **Biopsy:**

- Biopsy can be used to evaluate **malignancy**, **histologic grade**, and sometimes histologic type.
- The **incision or core track** should be placed in a location that can be **completely excised** at the time of definitive resection with minimal sacrifice of overlying skin.
- **Excisional biopsy** should be avoided, **especially for lesions >3 cm** in size, as contamination of surrounding tissue may require the definitive resection to be more extensive.

Soft Tissue Sarcoma (DIAGNOSIS AND STAGING)

- **Imaging:**

- Imaging studies for soft tissue sarcoma vary, depending to some extent on the site.
- They involve evaluation of both the **primary lesion** and **potential sites of metastasis**.
- Evaluation of primary lesions in the extremity, head, and neck is predominantly by either **CT or MRI**.
- Although **MRI** provides some increased definition, a Radiology Diagnostic Oncology Group study comparing these modalities **showed no benefit of MRI over CT**.
- For the primary sarcomas in the abdomen, chest, or retroperitoneum, a spiral CT scan is preferable because air–tissue interface and motion artifacts often degrade MRI quality. In addition, spiral CT allows both the primary tumor and potential for metastasis to be assessed simultaneously. Especially in this era of cost containment, imaging of the same entity by multiple modalities is not required.

Soft Tissue Sarcoma(nccn)

- **PET scans** may be useful in **staging**, **prognostication**, **grading**, and determining histopathologic **response to chemotherapy**.
- The maximum standardized uptake value (**SUVmax**) of F18-deoxyglucose has been shown to correlate with **tumor grade** and **prognostication**.
- In a retrospective study, tumor SUVmax determined by PET was an independent **predictor of survival** and disease progression.
- Schuetze and colleagues reported that the pretreatment SUVmax and change in SUVmax after preoperative chemotherapy independently identified patients with a high risk of recurrence.
- Patients with a change in the SUVmax of **40% or more** in response to chemotherapy were at a significantly lower risk of recurrence and death after complete resection and postoperative RT; the projected 5-year RFS rate for this group of patients was 80% compared to 40% for those with a less than 40% reduction in SUVmax.
-

Responder
Nonresponder

Soft Tissue Sarcoma (DIAGNOSIS AND STAGING)

- Further prospective studies across all histologic types of sarcoma are needed to determine if FDG-PET is sufficiently specific and accurate in determining chemotherapy response.

- The **current role of PET** seems to be primarily in the identification of **unsuspected sites of metastasis** in patients with recurrent high-grade tumors.

Soft Tissue Sarcoma (DIAGNOSIS AND STAGING)

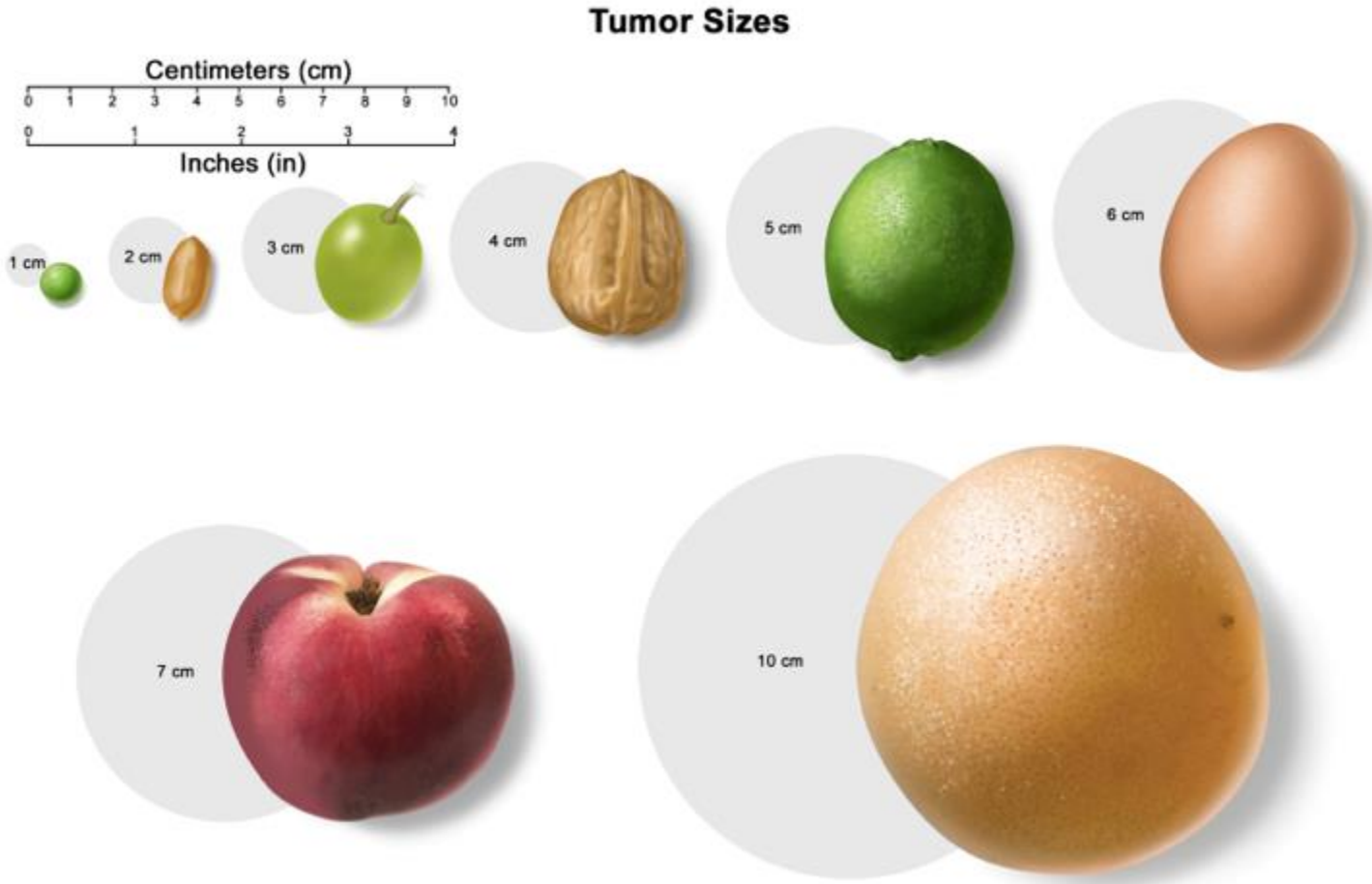
- Patients with visceral and retroperitoneal lesions should have their liver imaged as part of the initial abdominal CT or MRI.
- For low-grade or small superficial high-grade extremity sarcomas, imaging for metastasis is less important, and **simple chest radiography** will suffice.
- Conversely, for patients with deep or large high-grade extremity lesions, for which the risk of metastatic disease is significant, more extensive evaluation with a CT scan of the chest is often preferred.
- Although **CT is the most commonly used** modality to evaluate pulmonary metastases, it is more expensive than radiographs, delivers a higher radiation dose, and may give false-positive results because of small, indeterminate pulmonary nodules.

TABLE 60.3

Prognostic Stage Groups According to American Joint Committee on Cancer Staging System (8th Edition, 2017)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor <5 cm in greatest dimension
T2	Tumor 5 cm to 10 cm in greatest dimensi
T3	Tumor >10 cm to 15 cm in greatest dimer
T4	Tumor > 15 cm in greatest dimension

Stage	Grade	Tumor	Nodes	Metastasis
IA	G1, GX	T1	N0	M0
IB	G1, GX	T2, T3, T4	N0	M0
II	G2, G3	T1	N0	M0
IIIA	G2, G3	T2	N0	M0
IIIB	G2, G3	T3, T4	N0	M0
IV	G any	T any	N1	M0
IV	G any	T any	N any	M1



American Joint Committee on Cancer (AJCC) Staging System for Soft Tissue Sarcoma of the Trunk and Extremities (8th ed, 2017)

Table 3. **Definitions for T, N, M**

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence for primary tumor
T1	Tumor 5 cm or less in greatest dimension
T2	Tumor more than 5 cm and less than or equal to 10 cm in greatest dimension
T3	Tumor more than 10 cm and less than or equal to 15 cm in greatest dimension
T4	Tumor more than 15 cm in greatest dimension
N	**Regional Lymph Nodes**
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis
M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis
G	**Definition of Grade** **FNCLCC Histologic Grade - See Histologic Grade (G)**
GX	Grade cannot be assessed
G1	Total differentiation, mitotic count and necrosis score of 2 or 3
G2	Total differentiation, mitotic count and necrosis score of 4 or 5
G3	Total differentiation, mitotic count and necrosis score of 6, 7, or 8

Table 4. **AJCC Anatomic Stage/Prognostic Groups**

	T	N	M	G
Stage IA	T1	N0	M0	G1, GX
Stage IB	T2	N0	M0	G1, GX
	T3	N0	M0	G1, GX
	T4	N0	M0	G1, GX
Stage II	T1	N0	M0	G2, G3
Stage IIIA	T2	N0	M0	G2, G3
Stage IIIB	T3	N0	M0	G2, G3
	T4	N0	M0	G2, G3
Stage IV	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

Histologic Grade (G)

The FNCLCC grade is determined by three parameters: differentiation, mitotic activity, and extent of necrosis. Each parameter is scored as follows: differentiation (1-3), mitotic activity (1-3), and necrosis (0-2). The scores are added to determine the grade.

Tumor Differentiation

1	Sarcomas closely resembling normal adult mesenchymal tissue (e.g., low-grade leiomyosarcoma)
2	Sarcomas for which histologic typing is certain (e.g., myxoid/round cell liposarcoma)
3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, soft tissue osteosarcoma, Ewing sarcoma/primitive neuroectodermal tumor (PNET) of soft tissue

Mitotic Count

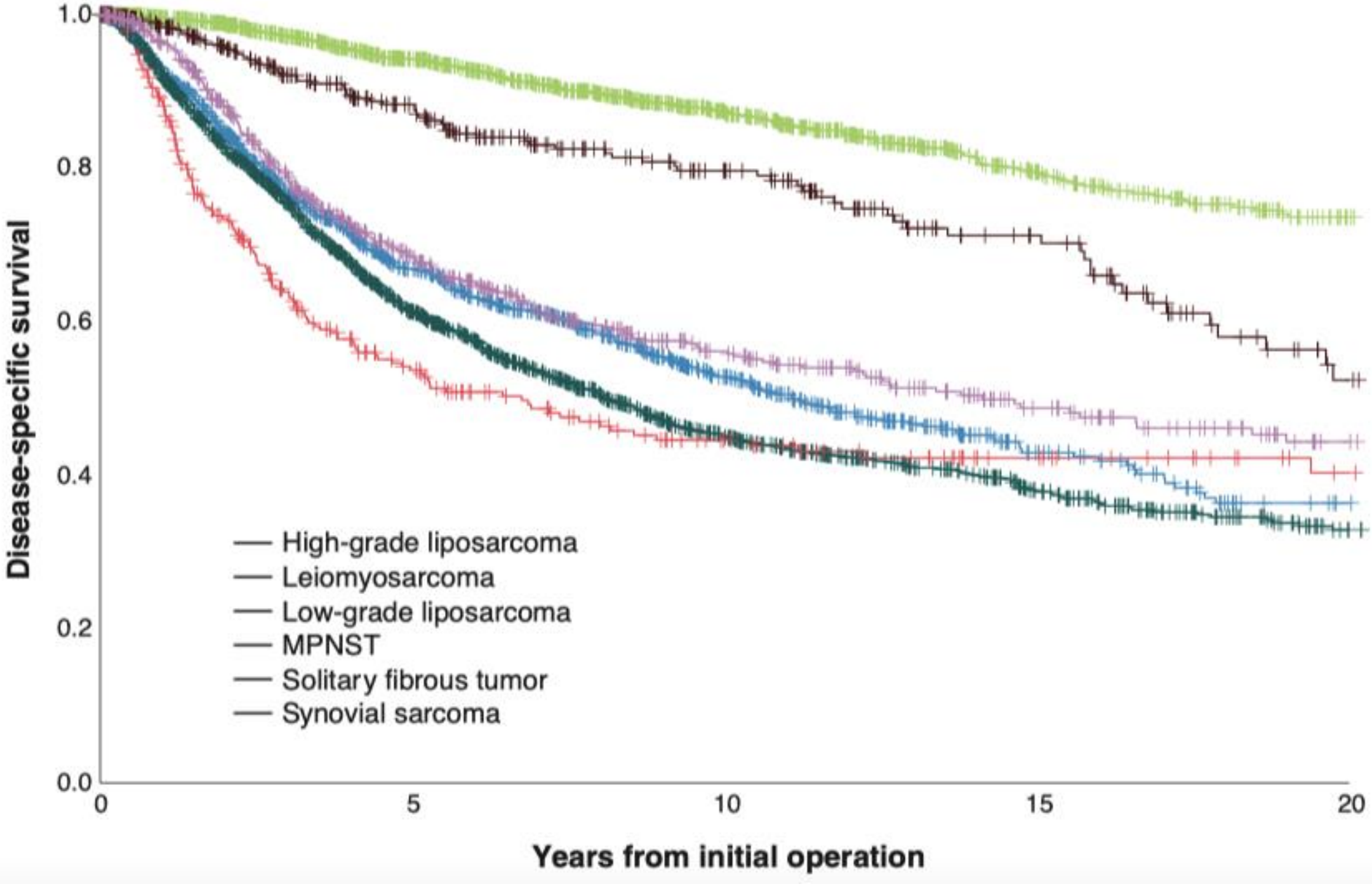
In the most mitotically active area of the sarcoma, 10 successive high-power fields (HPF; one HPF at 400× magnification= 0.1734 mm^2) are assessed using a 40× objective.

1	0-9 mitoses per 10 HPF
2	10-19 mitoses per 10 HPF
3	≥20 mitoses per 10 HPF

Tumor Necrosis

Evaluated on gross examination and validated with histologic sections.

0	No necrosis
1	<50% tumor necrosis
2	≥50% tumor necrosis


1.0
0.8
0.6
0.4
0.2
0.0
Disease-specific survival
0
5
10
15
20
Years from initial operation
High-grade liposarcoma
Leiomyosarcoma
Low-grade liposarcoma
MPNST
Solitary fibrous tumor
Synovial sarcoma

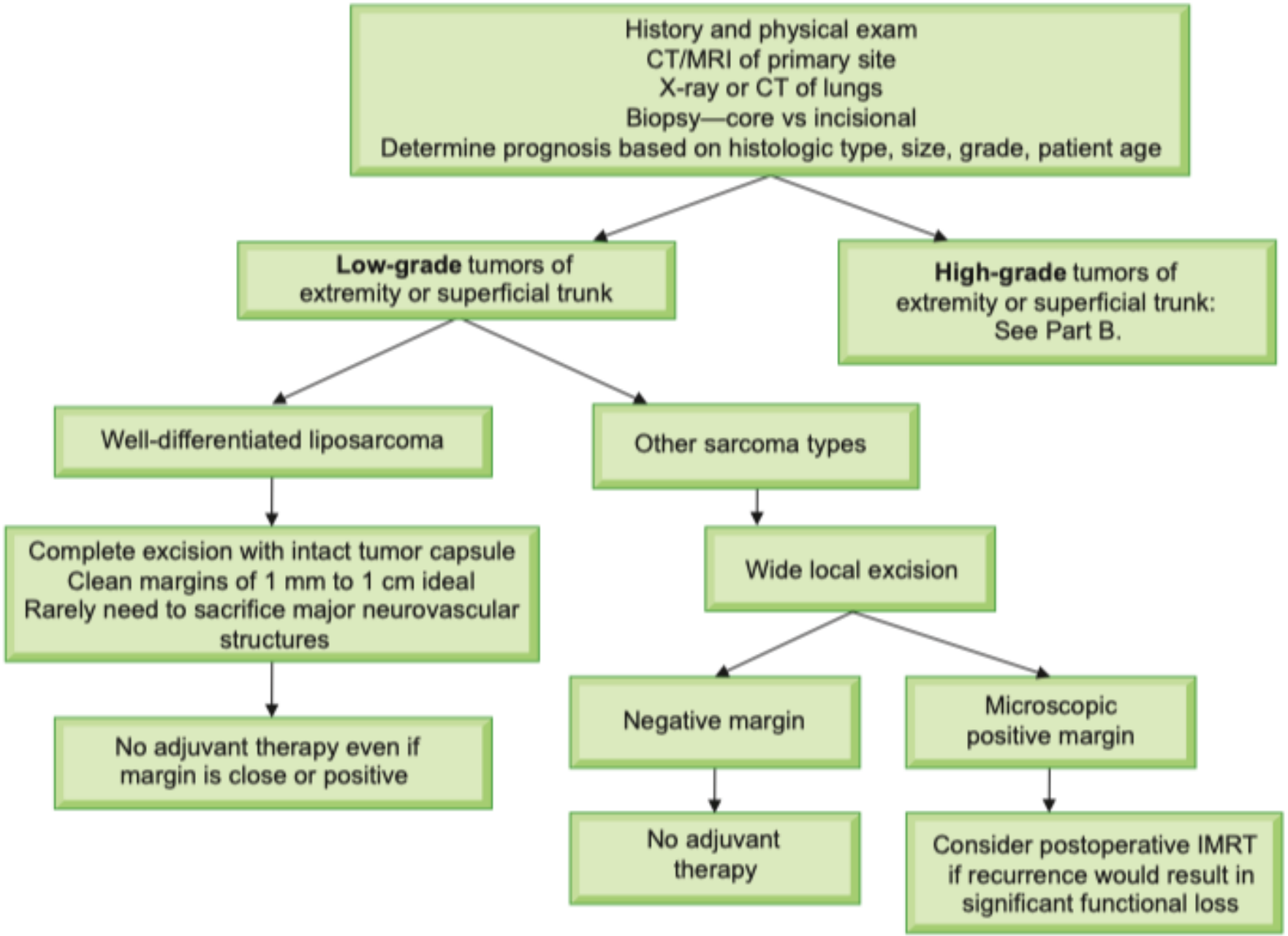
Soft Tissue Sarcoma
(Management of Extremity and Truncal Sarcoma)

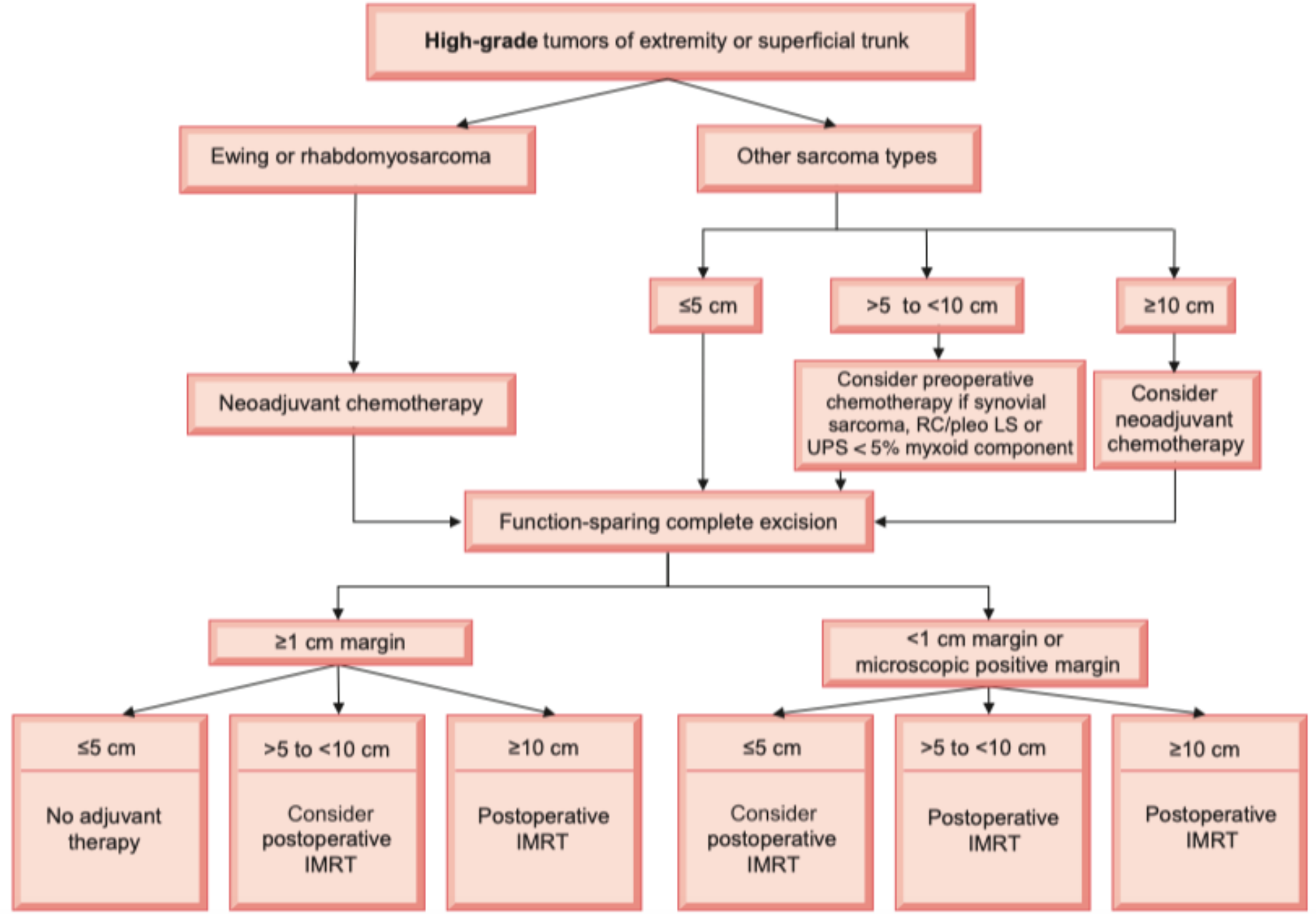
- **Surgical Management of Primary Localized Disease**

- Although **surgery** remains the principal therapeutic modality in soft tissue sarcoma, the extent of surgery required, along with the **optimum** combination of **radiotherapy** and **chemotherapy**, remains **controversial**.
- The individual patient's clinical and pathologic characteristics—particularly the pattern of spread expected for the patient's histologic subtype—should be used to design the most effective treatment plan. Figure 60.7 shows a suggested algorithm for management of patients with extremity or truncal disease.

Soft Tissue Sarcoma (MANAGEMENT)

- Amputation should be reserved for tumors that cannot be resected by any other means, in patients without evidence of metastatic disease and with potential for good long-term functional rehabilitation.
- Instead, modern surgery for extremity or truncal tumors most often consists of wide en bloc resection.
- Historical attempts to resect all muscle bundles from origin to exertion have been supplanted by an encompassing resection, aiming to **obtain a 1-cm margin** of uninvolved tissue in all directions.
- **Two-centimeter margins** are employed for histologic subtypes with infiltrative borders (e.g., **DFSP** or **myxofibrosarcoma**).
- For certain low-grade histologic types, however, even 1-cm margins are not required for excellent local control.
- For example, ALT/WDLSs of the extremities require only complete excision with a minimal surrounding margin because recurrence is rarely morbid in these patients and often does not occur even after a limited or microscopically positive margin excision.


History and physical exam
CT/MRI of primary site
X-ray or CT of lungs
Biopsy—core vs incisional
Determine prognosis based on histologic type, size, grade, patient age
Low-grade tumors of extremity or superficial trunk
High-grade tumors of extremity or superficial trunk: See Part B.
Well-differentiated liposarcoma
Other sarcoma types
Complete excision with intact tumor capsule
Clean margins of 1 mm to 1 cm ideal
Rarely need to sacrifice major neurovascular structures
Wide local excision
No adjuvant therapy even if margin is close or positive
Negative margin
Microscopic positive margin
No adjuvant therapy
Consider postoperative IMRT if recurrence would result in significant functional loss


High-grade tumors of extremity or superficial trunk
Ewing or rhabdomyosarcoma
Other sarcoma types
≤5 cm
>5 to <10 cm
≥10 cm
Neoadjuvant chemotherapy
Consider preoperative chemotherapy if synovial sarcoma, RC/pleo LS or UPS < 5% myxoid component
Consider neoadjuvant chemotherapy
Function-sparing complete excision
≥1 cm margin
<1 cm margin or microscopic positive margin
≤5 cm
No adjuvant therapy
>5 to <10 cm
Consider postoperative IMRT
≥10 cm
Postoperative IMRT
≤5 cm
Consider postoperative IMRT
>5 to <10 cm
Postoperative IMRT
≥10 cm
Postoperative IMRT

NCCN Guidelines Version 2.2022
Extremity/Body Wall, Head/Neck

NCCN Guidelines Index
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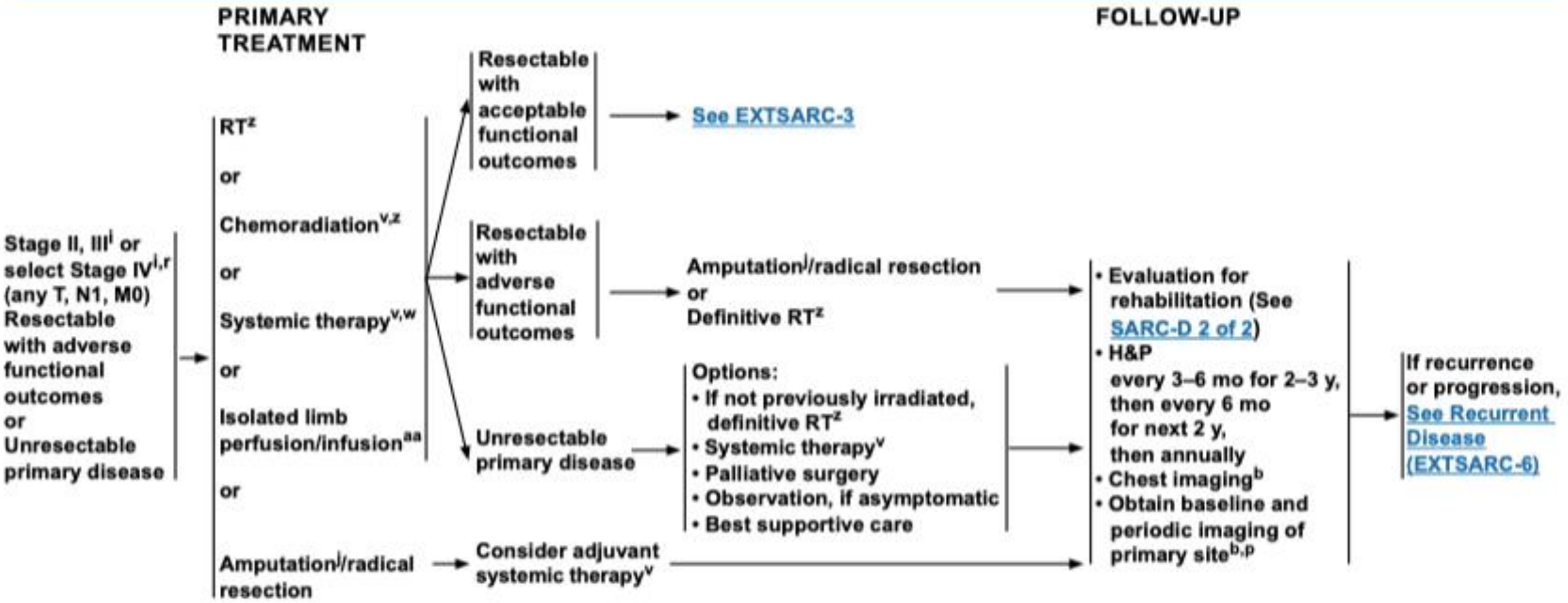
Discussion



Soft Tissue Sarcoma(nccn)

- The anatomic site of the primary disease represents an important variable that influences treatment and outcome.
- Extremities (43%), the trunk (10%), visceral (19%), retroperitoneum (15%), or head and neck (9%) are the most common primary sites.

- Prior to initiation of treatment, all patients should be evaluated and managed by a **multidisciplinary team** with extensive expertise and experience in the treatment of STS.
- Because STS is rare and often complex, adherence to evidence-based recommendations is particularly important.

Soft Tissue Sarcoma(nccn)

- **Large stage II or III high-grade extremity** resectable tumors (greater than 8–10 cm) that are at high risk for LR and metastases should be considered for **preoperative** and **postoperative** therapy.
-

Soft Tissue Sarcoma(nccn)

- **Stage II-III**
- Treatment options should be decided by a **multidisciplinary team** with extensive experience in the treatment of patients with STS, based on the patient's age, performance status, comorbidities, location, and histologic subtype of the tumor
- **Preoperative chemoradiation** has been shown to improve **OS**, **DFS**, and **local control** rates in patients with high-grade STS of extremity and trunk, although acute reactions must be considered.
- An earlier randomized study showed that **preoperative chemotherapy** was **not associated** with a major survival benefit for patients with high-grade tumors.

Soft Tissue Sarcoma(nccn)

- **Surgery followed by RT** (**category 1**) with or without postoperative chemotherapy is the primary treatment for patients with stage IIIA (T2, N0, M0, G2-3) or IIIB (T3-4, N0, M0, G2-3) tumors that are resectable with acceptable functional outcomes.
- The impact of RT was analyzed in a SEER cohort of 2606 patients with stage III soft-tissue extremity sarcoma. Similarly to smaller prospective studies and reviews, RT was associated with a significant 5-year survival benefit (65% vs. 60%, P = .002).
- However, the timing of RT (ie, **preoperative** vs. **postoperative**) was not a significant factor for survival.
- Since there are only limited and conflicting data regarding the potential benefits of postoperative chemotherapy for **stage II or III patients**, postoperative **chemotherapy** is included as a **category 2B recommendation**.
- **Preoperative RT** (**category 1**), **preoperative chemotherapy** (**category 2B**), or chemoradiation (category 2B) are also included as options for this group of patients.

SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA SUBTYPES[a,b,c,d]

Soft Tissue Sarcoma Subtypes with Non-Specific Histologies
(Regimens Appropriate for General Soft Tissue Sarcoma[e,f]; see other sections for histology-specific recommendations)

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Neoadjuvant/ Adjuvant Therapy	• AIM (doxorubicin, ifosfamide, mesna)[1-4] • Ifosfamide, epirubicin, mesna[5]	• AD LMS only (doxorubicin, dacarbazine)[1,2,6,7] if ifosfamide is not considered appropriate • Doxorubicin[1,2,8,9] • Gemcitabine and docetaxel[10,11]	• Ifosfamide[5,9,10-14] • Trabectedin (for myxoid liposarcoma)[15]
First-Line Therapy Advanced/Metastatic	• Anthracycline-based regimens: ▸ Doxorubicin[1,2,8,9] ▸ Epirubicin[16] ▸ Liposomal doxorubicin[17] ▸ AD (doxorubicin, dacarbazine)[1,2,6,7,18] ▸ AIM (doxorubicin, ifosfamide, mesna)[1-4,8] ▸ Ifosfamide, epirubicin, mesna[5] • *NTRK* gene fusion-positive sarcomas only ▸ Larotrectinib[g,19] ▸ Entrectinib[h,20]	• Gemcitabine-based regimens: ▸ Gemcitabine ▸ Gemcitabine and docetaxel[10,11] ▸ Gemcitabine and vinorelbine[13] ▸ Gemcitabine and dacarbazine[14]	• Pazopanib[j,21] (patients ineligible for IV systemic therapy or patients who are not candidates for anthracycline-based regimens) • MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[1,2,22,23]
Subsequent Lines of Therapy for Advanced/Metastatic Disease	• Pazopanib[i,j,21] • Eribulin[i,24] (category 1 recommendation for liposarcoma, category 2A for other subtypes • Trabectedin[i,25-27] (category 1 recommendation for liposarcoma and leiomyosarcoma, category 2A for other subtypes)	• Dacarbazine[14] • Ifosfamide[5,9,10-13,28] • Temozolomide[i,29] • Vinorelbine[i,30] • Regorafenib[j,31] • Gemcitabine-based regimens (if not given previously): ▸ Gemcitabine ▸ Gemcitabine and docetaxel[10,11] ▸ Gemcitabine and vinorelbine[13] ▸ Gemcitabine and dacarbazine[14] ▸ Gemcitabine and pazopanib (category 2B)[32]	• Pembrolizumab[k,33,70] (for myxofibrosarcoma, undifferentiated pleomorphic sarcoma [UPS], cutaneous angiosarcoma, and undifferentiated sarcomas)

Footnotes and references see SARC-F, 7 of 11

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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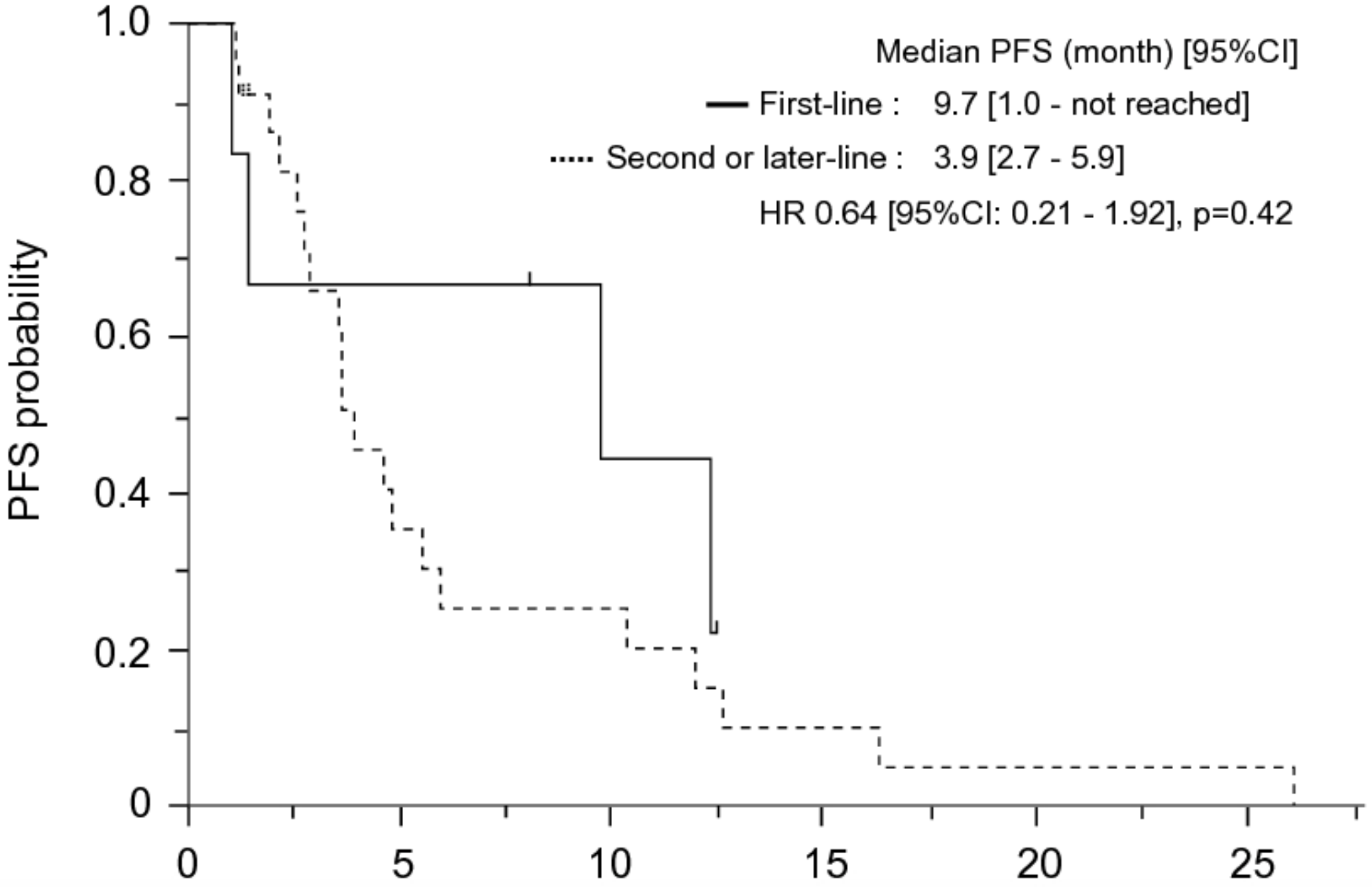
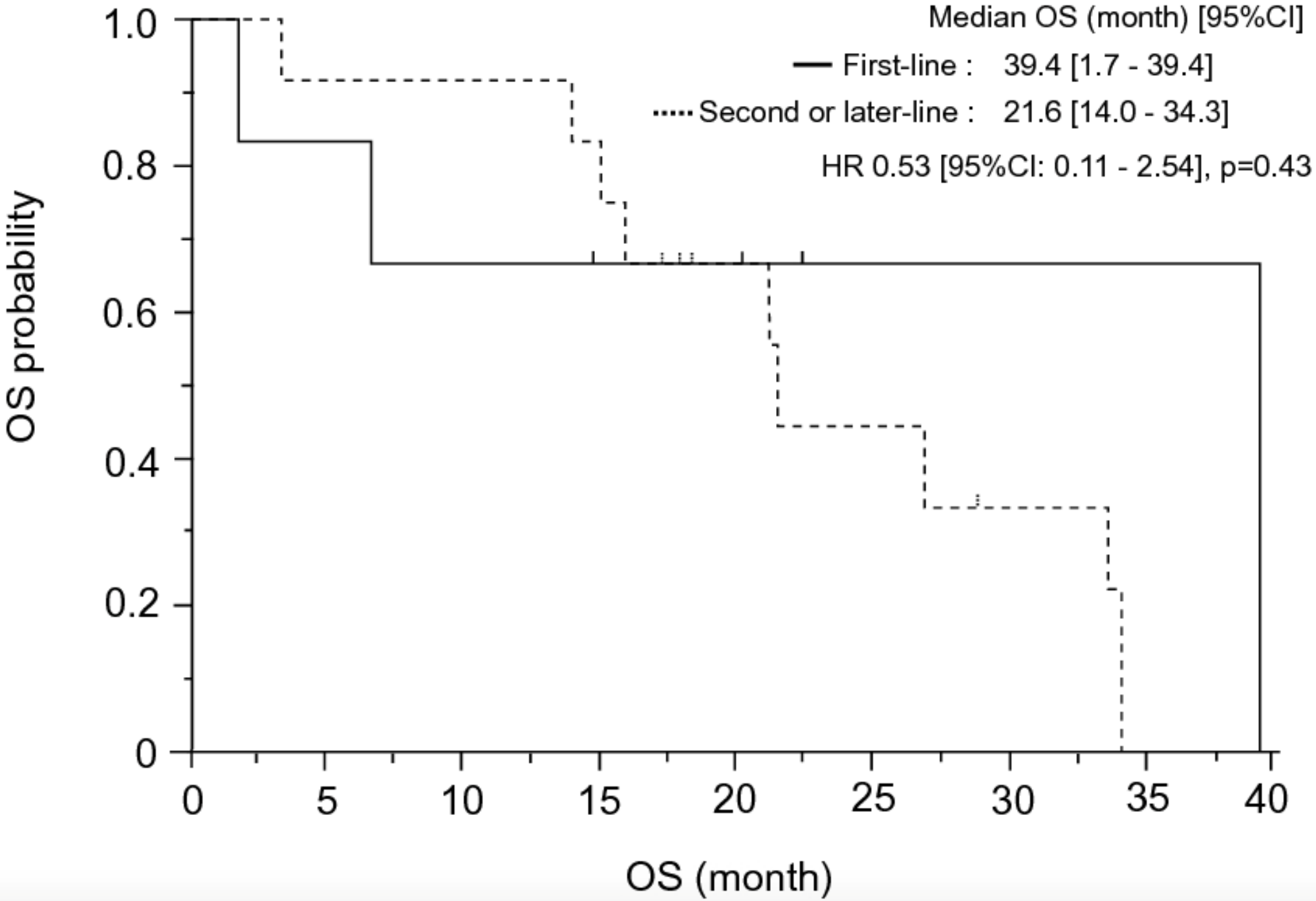
Check for updates

OPEN

Eribulin as a first-line treatment for soft tissue sarcoma patients with contraindications for doxorubicin

Kenji Tsuchihashi[1], Hitoshi Kusaba[1], Tomoyasu Yoshihiro[2], Toshifumi Fujiwara[3],


Median PFS (month) [95%CI]
First-line : 9.7 [1.0 - not reached]
Second or later-line : 3.9 [2.7 - 5.9]
HR 0.64 [95%CI: 0.21 - 1.92], p=0.42
PFS probability
1.0
0.8
0.6
0.4
0.2
0
0
5
10
15
20
25


Median OS (month) [95%CI]
First-line : 39.4 [1.7 - 39.4]
Second or later-line : 21.6 [14.0 - 34.3]
HR 0.53 [95%CI: 0.11 - 2.54], p=0.43
OS probability
1.0
0.8
0.6
0.4
0.2
0
0
5
10
15
20
25
30
35
40
OS (month)

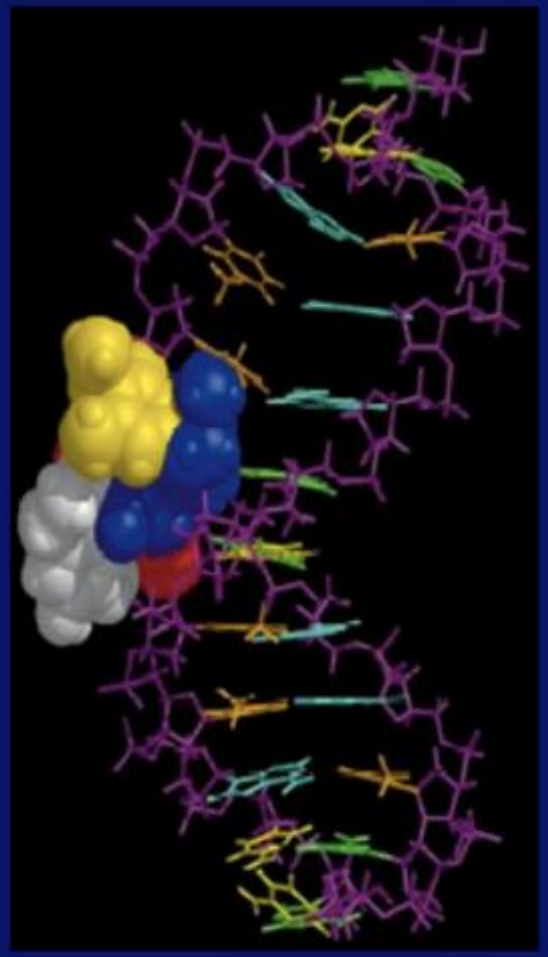
Soft Tissue Sarcoma(nccn)

- **Trabectedin** is a **novel DNA-binding agent** that has shown objective responses in phase II and III studies of patients with advanced STS.
- Recent phase III data from a randomized, multicenter trial revealed a 2.7month PFS benefit versus dacarbazine in metastatic **liposarcoma** (**LPS**) or **LMS** that progressed after anthracycline-based therapy.
- However, the study **failed** to demonstrate an **overall survival** advantage for trabectedin over dacarbazine.

Soft Tissue Sarcoma(nccn)

- Another study supported the efficacy of **trabectedin** in **translocation-related sarcoma**.
- A phase III trial comparing trabectedin and doxorubicin-based chemotherapy revealed that neither arm showed superiority for PFS and OS; however, the trial was underpowered.
- Preliminary results from the randomized phase III T-SAR trial revealed a PFS benefit for trabectedin over best supportive care in both “L-type” (LPS and LMS) and non–L-type pretreated advanced sarcoma.
- However, trabectedin plus doxorubicin failed to demonstrate superiority over doxorubicin alone in a randomized phase II study of patients with advanced STS.
- **Trabectedin** is included for palliative therapy as a **category 1** recommendation for **LPS** and **LMS** (L-type) and as **category 2A** for non–L-type sarcomas.

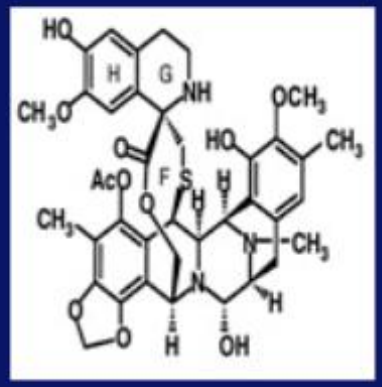
Not all Molecular Targeted Agents are Rationally Designed – but the clinical evaluation can be rational and targeted



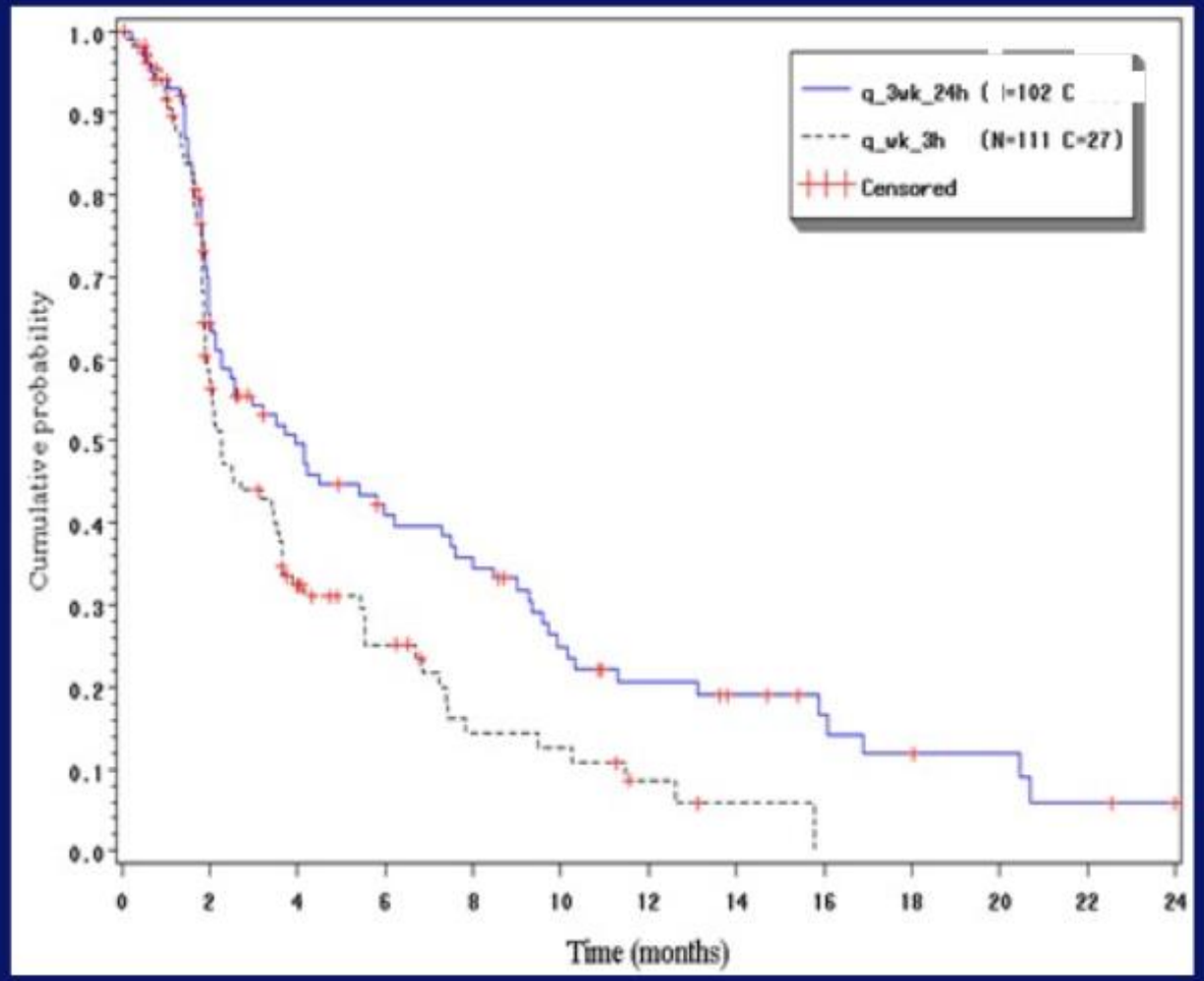
Sea Tunicate, *Ecteinascidia Turbinata*

- Binds to DNA minor groove, bending the helix
- Interacts with transcription factors and other DNA binding proteins
- Major activity in myxoid/round cell liposarcoma with TLS/CHOP fusion oncoprotein (DNA binding protein)

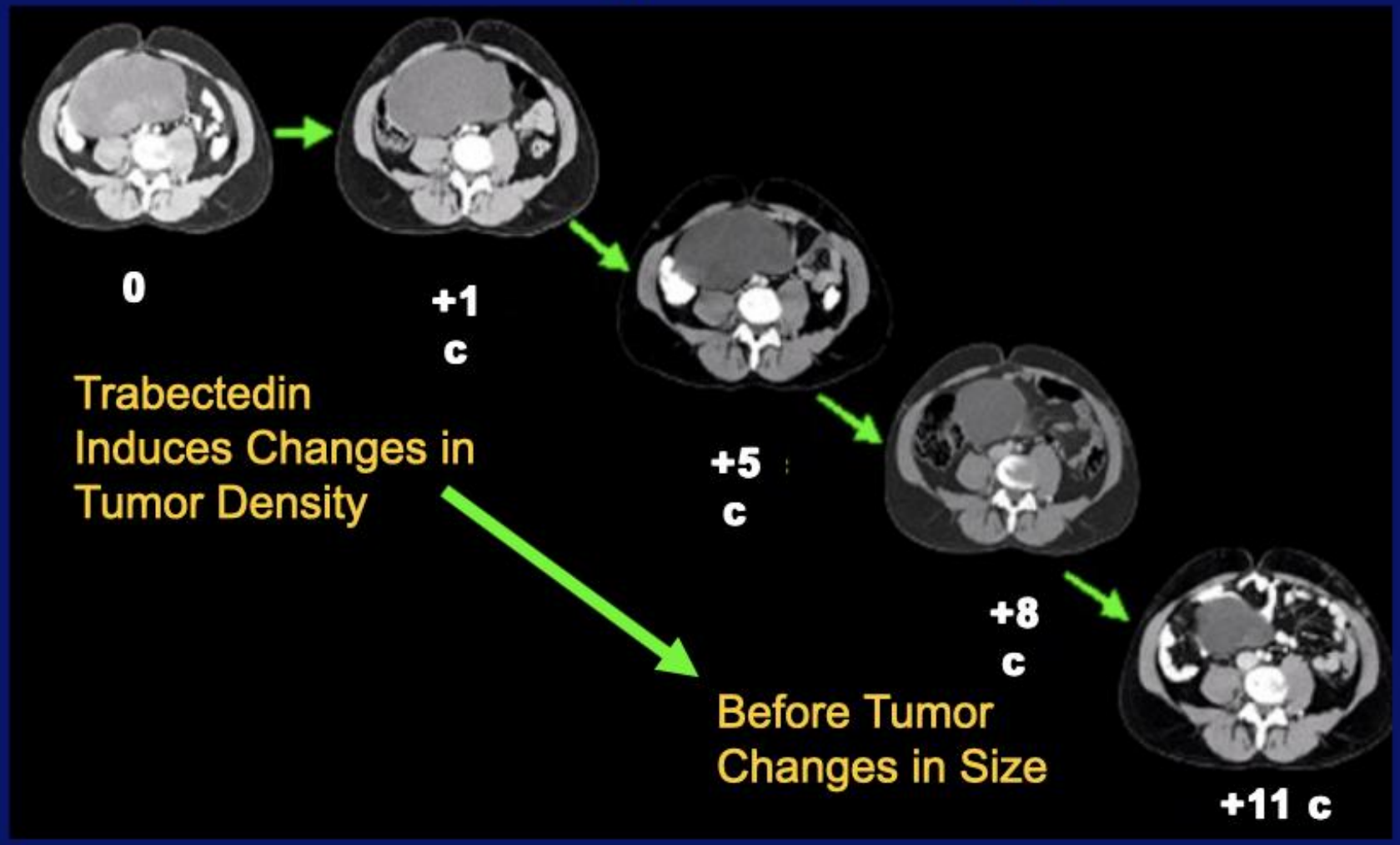
Ecteinascidin-743
(Trabectedin),
a tetrahydroisoquinoline
alkaloid
(MW = 762)



Trabectedin Improves Time to Progression in Advanced Histopathologically Confirmed Leiomyosarcomas and Liposarcomas (Independent Review)



Efficacy of Trabectedin (ecteinascidin-743) in Advanced Pretreated Myxoid Liposarcomas: a Retrospective Study

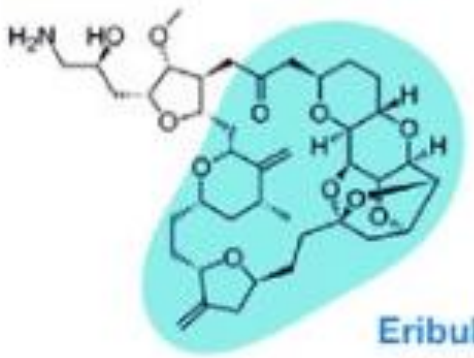


Grosso, Jones, Demetri, et al, Lancet Oncology 2007.

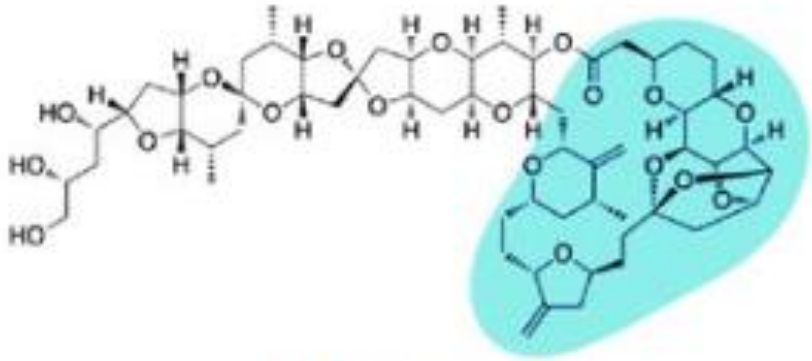
Soft Tissue Sarcoma(nccn)

- **Eribulin** is a **novel microtubule-inhibiting agent** that has been evaluated as a single-agent therapy for STS, including **LMS**, **adipocytic sarcoma**, **synovial sarcoma**, and other tumor types.
- Recent data from a phase III trial compared the **survival benefit** of eribulin and dacarbazine in 452 patients with advanced LMS or LPS, revealing a median OS of 13.5 months and 11.5 months, respectively (HR, 0.77; 95% CI, 0.62–0.95; P = .017).
- A subgroup analysis demonstrated that the survival benefit was limited to LPS, and therefore eribulin is included for **palliative therapy** as a **category 1 recommendation** for LPS and as category 2A for other subtypes.

Eribulin
structural simplification of a natural product

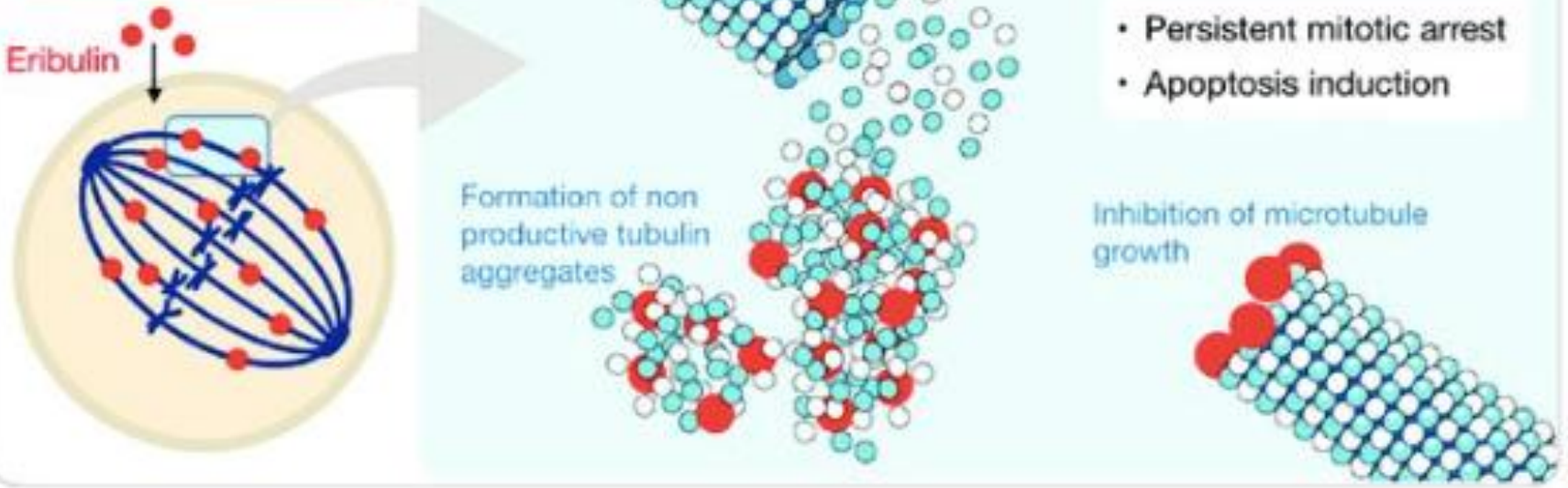


Eribulin



Halichondrin B
isolated from marine sponge *Halichondria okadai*

Mechanisms of action and effects of Eribulin




7

Soft Tissue Sarcoma(nccn)

- **Targeted Therapy:**

- More recently, a number of targeted therapies have shown promising results in patients with certain histologic types of advanced or metastatic STS.

Soft Tissue Sarcoma(nccn)

- **Pazopanib**, a multitargeted **tyrosine kinase inhibitor** (**TKI**), has demonstrated single-agent activity in patients with **advanced STS subtypes except LPS**.
- In a phase III study (EORTC 62072), 369 patients with metastatic non-lipogenic STS who had **failed** at least one **anthracycline-based chemotherapy** regimen were randomized to either pazopanib or placebo.
- **Pazopanib** significantly prolonged median **PFS** (4.6 vs.1.6 months for placebo; P < .0001) and there was also a trend toward **improved OS** (12.5 and 11 months, respectively; P = .25), although this was **not statistically** significant.
- Health-related quality-of-life measures did not improve or decline with the PFS benefit. 137 Pooled data from individuals who received pazopanib in phase II and III trials (n = 344) revealed a subset of long-term responders/survivors presenting at baseline with good performance status, low-/intermediate-grade primary tumor, and normal hemoglobin level.
- Results from the open-label phase II EPAZ study found that **pazopanib** demonstrated **non-inferior PFS** compared with **doxorubicin** (4.4 vs. 5.3 months, respectively) as a f**irst-line** treatment in elderly patients with advanced/metastatic STS.
- The **guidelines** have included **pazopanib** as a **first-line therapy** option for those with advanced or metastatic disease who are **ineligible** for intravenous (**IV**) systemic therapy or are not candidates for **anthracycline-based** regimens, and as a **subsequent-line treatment** option for patients with advanced or metastatic non-lipogenic STS as palliative therapy (SARC-F 1 of 11).
- **Pazopanib** in combination with **gemcitabine** is a category 2B subsequentline treatment option for advanced/metastatic disease.

Soft Tissue Sarcoma(nccn)

- The randomized, **phase II REGOSARC trial** examined regorafenib, a multitargeted **tyrosine kinase inhibitor** approved for treating GIST, in cohorts of patients with advanced LPS, LMS, synovial sarcoma, and other non-GIST STS subtypes (REGOSARC, n = 182).
- Compared to placebo, **regorafenib** significantly **extended PFS in all but** the **LPS** cohort.
- In patients with nonadipocytic STS, overall PFS for regorafenib and placebo treated patients was 4 months versus 1 month (HR, 0.36; P < .0001).
- **Regorafenib** is **included in the guidelines** as a treatment option for **advanced/metastatic non-adipocytic sarcomas**, as well as angiosarcoma.

Soft Tissue Sarcoma(nccn)

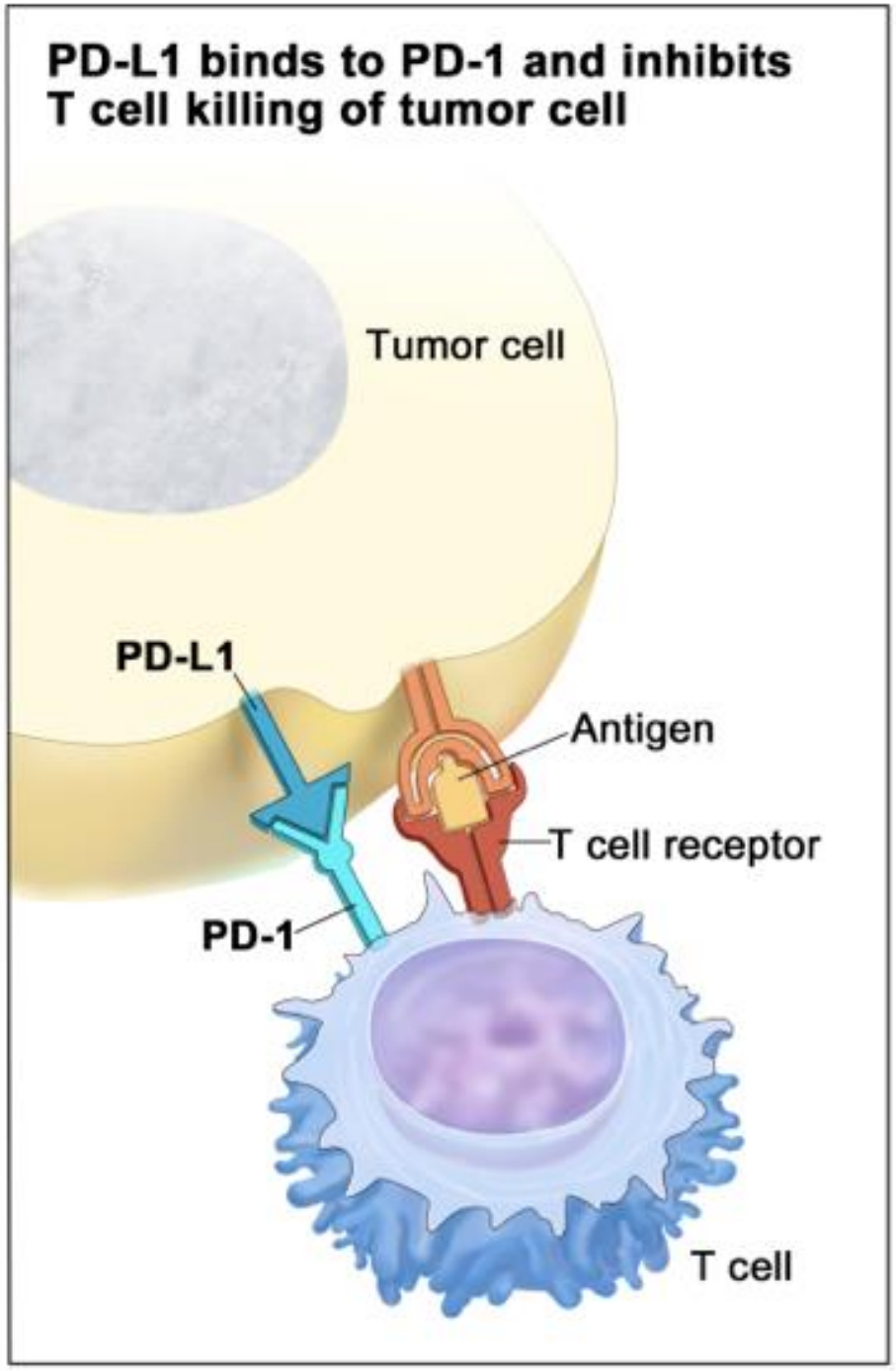
- Tropomyosin receptor kinase (**TRK**) inhibitors **larotrectinib** and **entrectinib** have demonstrated efficacy in patients with **neurotrophic receptor tyrosine kinase** (**NTRK**) **fusion-positive tumors**, and are therefore recommended as first-line treatment options for patients with advanced or metastatic NTRK gene fusion-positive sarcomas in the guidelines

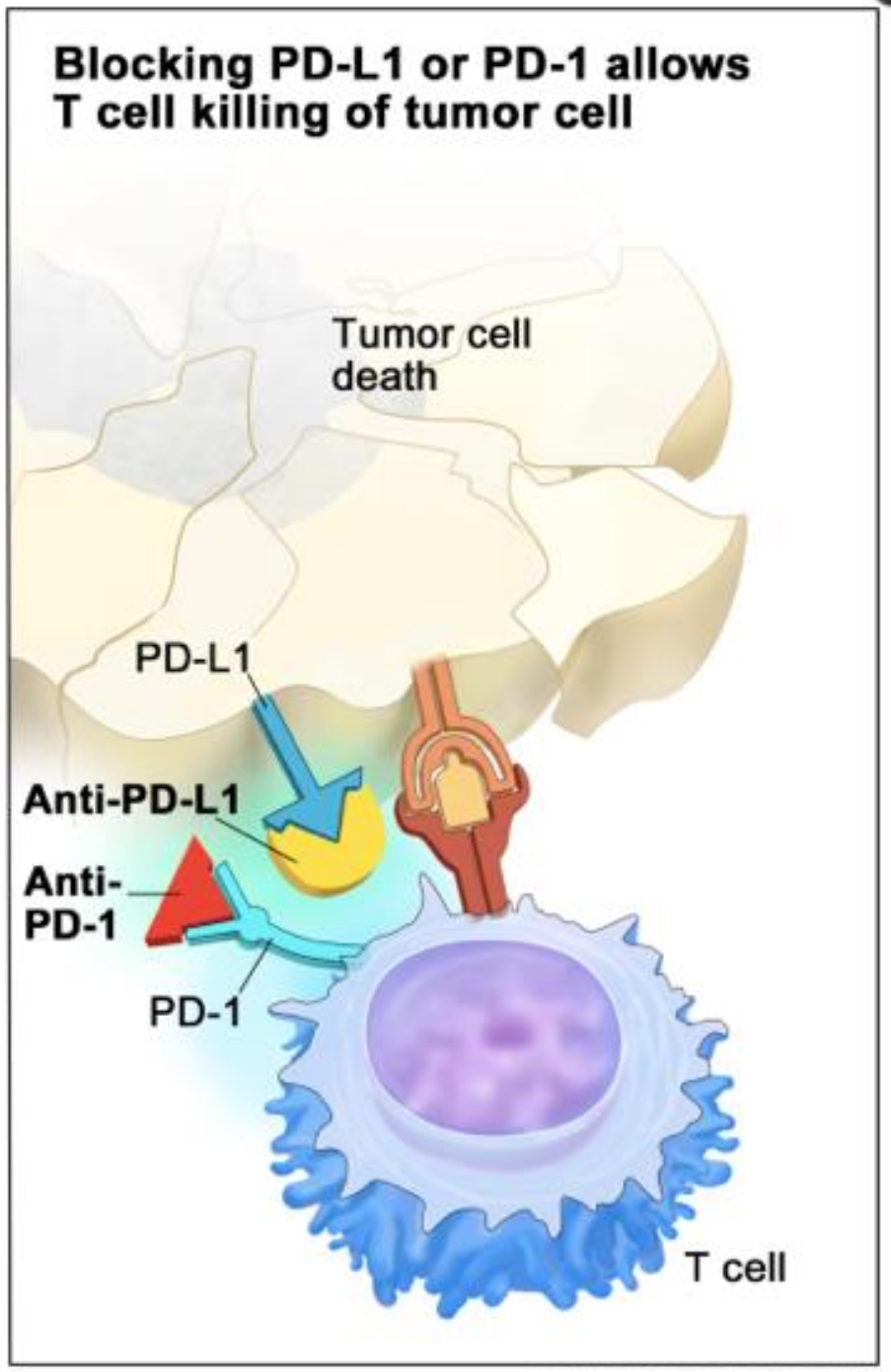
Soft Tissue Sarcoma

- **Immunotherapy**
- Immunotherapy is a treatment that uses the patient's immune system to fight cancer. Substances made by the body or made in a laboratory are used to boost, direct, or restore the body's natural defenses against cancer. This cancer treatment is a type of biologic therapy.
- Immune checkpoint inhibitor therapy is a type of immunotherapy. Some types of immune system cells, such as T cells, and some cancer cells have certain proteins, called checkpoint proteins, on their surface that keep immune responses in check. These checkpoints help keep immune responses from being too strong and sometimes can keep T cells from killing cancer cells. When these checkpoints are blocked, T cells can kill cancer cells better.
- Types of immune checkpoint inhibitor therapy include the following:
- CTLA-4 inhibitor therapy: CTLA-4 is a protein on the surface of T cells that helps keep the body's immune responses in check. When CTLA-4 attaches to another protein called B7 on a cancer cell, it stops the T cell from killing the cancer cell. CTLA-4 inhibitors attach to CTLA-4 and allow the T cells to kill cancer cells.
- Ipilimumab is a type of CTLA-4 inhibitor that is being studied to treat soft tissue sarcoma.

Soft Tissue Sarcoma

- PD-1 and PD-L1 inhibitor therapy: PD-1 is a protein on the surface of T cells that helps keep the body's immune responses in check. PD-L1 is a protein found on some types of cancer cells. When PD-1 attaches to PD-L1, it stops the T cell from killing the cancer cell. PD-1 and PD-L1 inhibitors keep PD-1 and PD-L1 proteins from attaching to each other. This allows the T cells to kill cancer cells.
- Pembrolizumab and nivolumab are PD-1 inhibitors that are used to treat progressive and recurrent soft tissue sarcoma.

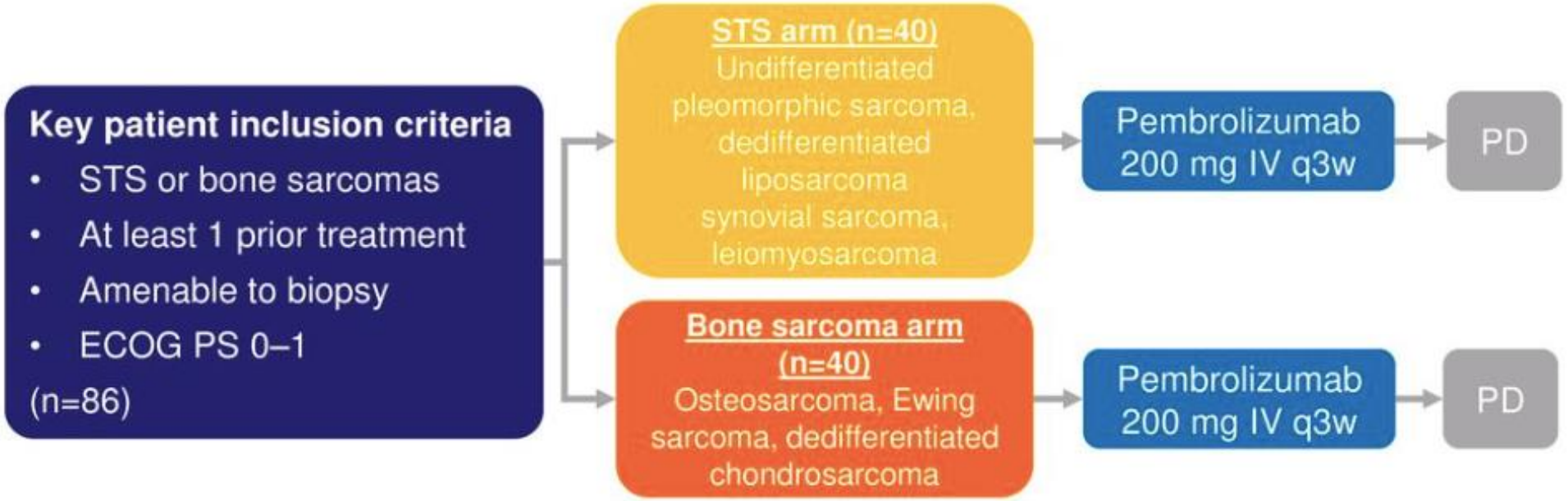




11008: Multicenter phase II study of pembrolizumab (P) in advanced soft tissue (STS) and bone sarcomas (BS): Final results of SARC028 and biomarker analyses – Burgess MA, et al

STUDY OBJECTIVE

- To evaluate the efficacy and biomarker correlations of response for pembrolizumab in patients with STS and bone sarcomas



Primary endpoint

- ORR (RECIST v1.1)

Secondary endpoints

- Safety, PFS, OS, response rate

Burgess MA, et al. J Clin Oncol 2017; 35 (Suppl): Abstr 11008

11008: Multicenter phase II study of pembrolizumab (P) in advanced soft tissue (STS) and bone sarcomas (BS): Final results of SARC028 and biomarker analyses – Burgess MA, et al

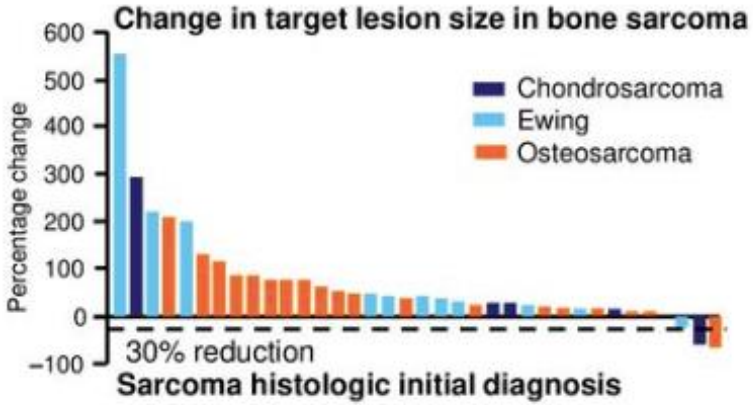
KEY RESULTS (CONT.)

Bone sarcoma: median PFS 8 weeks

	Events/n	Median, weeks	12-week estimate, %
Chondrosarcoma	4 / 5	8 (7,)	40 (0, 83)
Ewing	13 / 13	7 (7, 8)	15 (0, 35)
Osteosarcoma	22 / 22	8 (7, 18)	32 (12, 51)

Bone sarcoma: median OS 52 weeks

	Deaths/n	Median, weeks	12-week estimate, %
Chondrosarcoma	1 / 5	NR	80 (45, 100)
Ewing	10 / 13	41 (18, 65)	85 (65, 100)
Osteosarcoma	14 / 22	50 (31, 74)	91 (79, 100)



n (%)	Chondro	Ewing	Osteo	Total
PR	1 (20)	0	1 (5)	2 (5)
SD	1	2	6	9
PD	3	11	15	29

RECIST best response in bone sarcoma

CONCLUSIONS

- Pembrolizumab is generally well tolerated for patients with advanced sarcomas, and shows promising activity in UPS and LPS
- PD-L1 correlates with response in UPS
- Pembrolizumab is a potential treatment option in subsets of sarcomas (UPS, LPS)

Burgess MA, et al. J Clin Oncol 2017; 35 (Suppl): Abstr 11008

11007: A multi-center phase II study of nivolumab +/- ipilimumab for patients with metastatic sarcoma (Alliance A091401) – D'Angelo SP, et al

KEY RESULTS

	Nivolumab + ipilimumab (n=38)	Nivolumab (n=38)
BOR, n (%)		
CR	2 (5)	0
PR	5 (13)	3 (8)
SD	19 (50)	15 (39)
PD	10 (27)	20 (53)
Death/no assessment	2 (5)	0
ORR (CR + PR), n (%) [90%CI]	6 (16) [7, 29]	2 (5) [1, 15]
Clinical benefit rate (CR + PR + SD), % 90%CI)	29 (17, 43)	18 (1, 32)

	Nivolumab + ipilimumab (n=42)		Nivolumab (n=42)	
	Total (events)	Median (95%CI)	Total (events)	Median (95%CI)
OS	38 (20)	14.3 (9.6, NE)	38 (26)	10.7 (5.5, 15.4)
PFS	38 (30)	4.4 (2.6, 6.3)	38 (34)	2.1 (1.4, 4.4)

D'Angelo SP, et al. J Clin Oncol 2017; 35 (Suppl): Abstr 11007

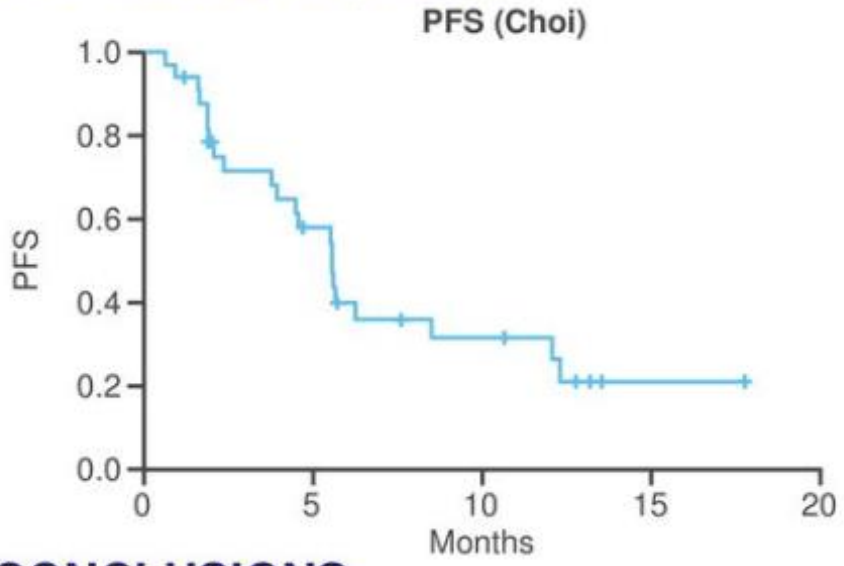
Soft Tissue Sarcoma(uptodate)

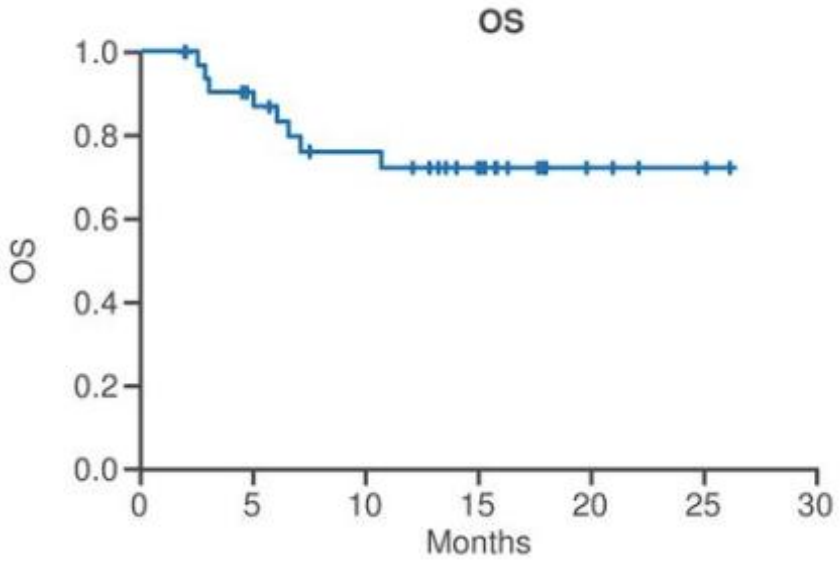
- Therapeutic nihilism is unwarranted


ممنون از توجه شما
04/17/2010

11003: Multi-institutional European single-arm phase II trial of pazopanib in advanced malignant/dedifferentiated solitary fibrous tumors (SFT): A collaborative Spanish (GEIS), Italian (ISG), and French (FSG) sarcoma groups study – Broto JM, et al

KEY RESULTS (CONT.)





CONCLUSIONS

- This is the first prospective study in malignant SFT
- Compared with CT, pazopanib showed superior response (Choi only), PFS and OS, with efficacy similar to previous anti-angiogenic agents (e.g. sunitinib)
- Choi response is an independent prognostic factor for OS for malignant SFT
- Compared with RECIST, use of Choi criteria allows more accurate response assessment

Broto JM, et al. J Clin Oncol 2017; 35 (Suppl): Abstr 11003