Visiting Professors: Investigator Perspectives on the Management of Soft Tissue Sarcoma

An Interactive Grand Rounds Series

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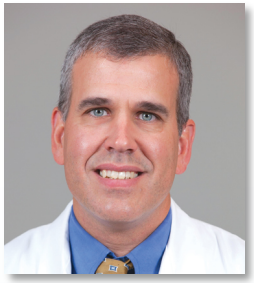

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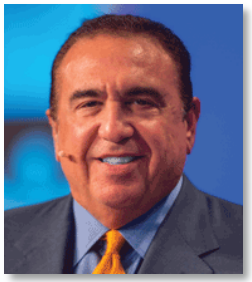

Project Chair
Neil Love, MD
Research To Practice
Miami, Florida

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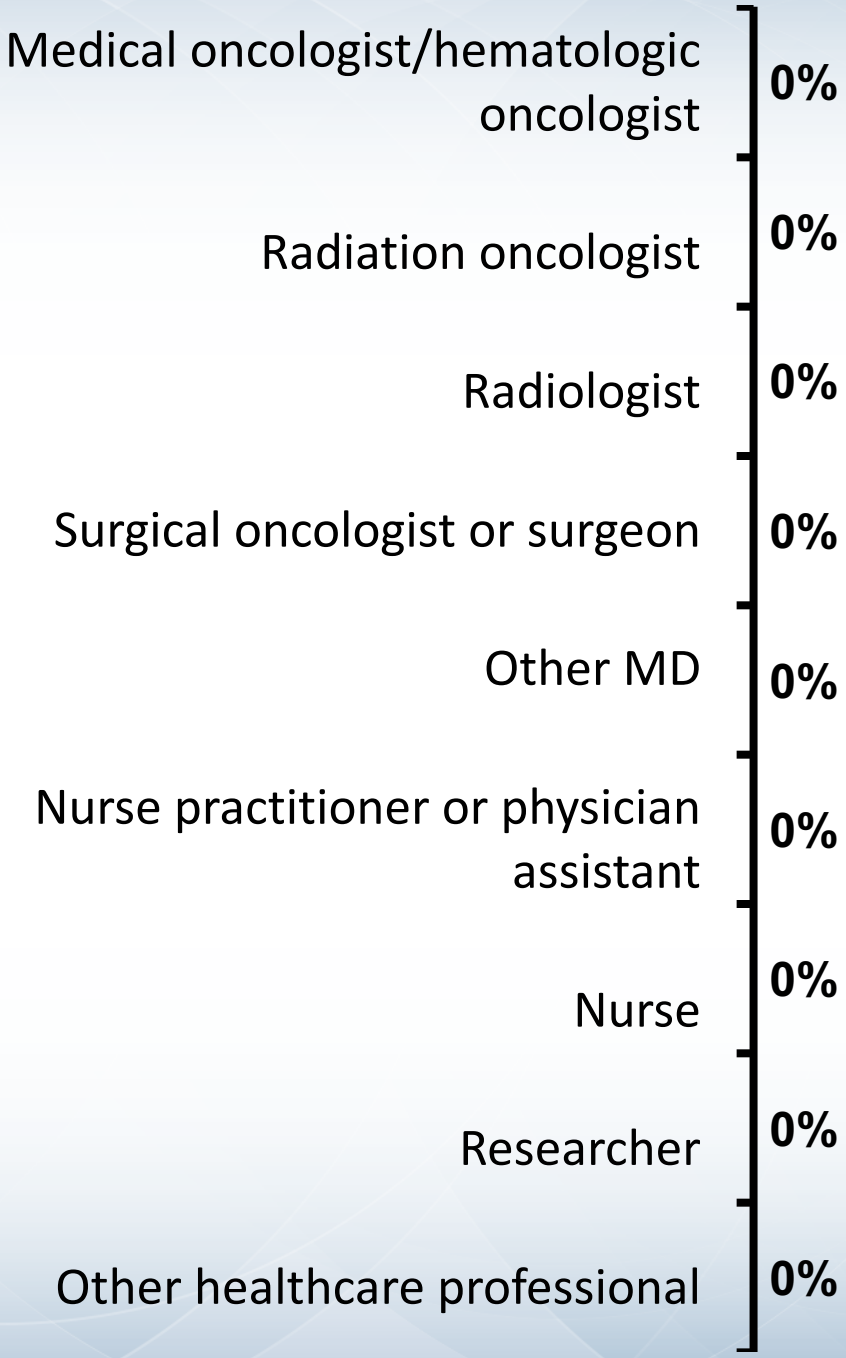
Which of the following best represents your clinical background?

1. Medical oncologist/hematologic oncologist
2. Radiation oncologist
3. Radiologist
4. Surgical oncologist or surgeon
5. Other MD
6. Nurse practitioner or physician assistant
7. Nurse
8. Researcher
9. Other healthcare professional



Management of Soft Tissue Sarcoma (STS)

MODULE 1: Overview of STS; Initial Workup and Classification

- Incidence, biology and histopathologic classification
- Biopsy technique; imaging workup
- Indications for involvement of specialized tertiary care providers

MODULE 2: Management of Localized Disease

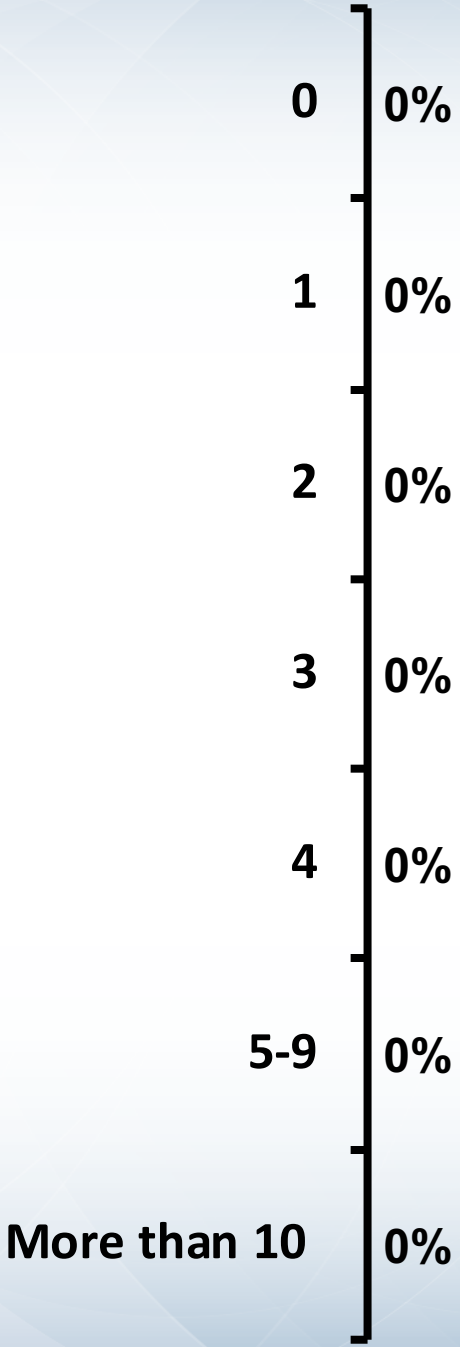
- Role of neoadjuvant/adjuvant radiation therapy
- Role of neoadjuvant/adjuvant chemotherapy

MODULE 3: Management of Metastatic STS

- Local treatment of oligometastatic disease
- Selection and sequencing of systemic treatments
- Investigational strategies and agents

Approximately how many patients with soft tissue sarcoma are currently in your practice?

1. 0
2. 1
3. 2
4. 3
5. 4
6. 5-9
7. More than 10



Overview of Sarcomas

- Estimated incidence of soft tissue sarcomas in the United States in 2019: 12,750
  - Approximately 0.7% of all new cancer cases in 2019
- Estimated deaths from soft tissue sarcomas in the United States in 2019: 5,270
  - Approximately 0.9% of all cancer deaths in 2019
- Sarcomas account for approximately 1% of all adult cancers and approximately 15% of pediatric cancers

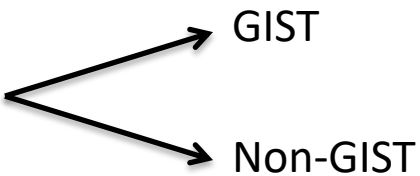
Siegel RL et al. *CA Cancer J Clin* 2018;68(1):7-30; *Cancer Facts and Figures* 2019 (American Cancer Society).

Sarcomas

Malignancies of connective tissue arising from mesodermal tissue

- About 1% of adult malignancies
- 15% of pediatric malignancies

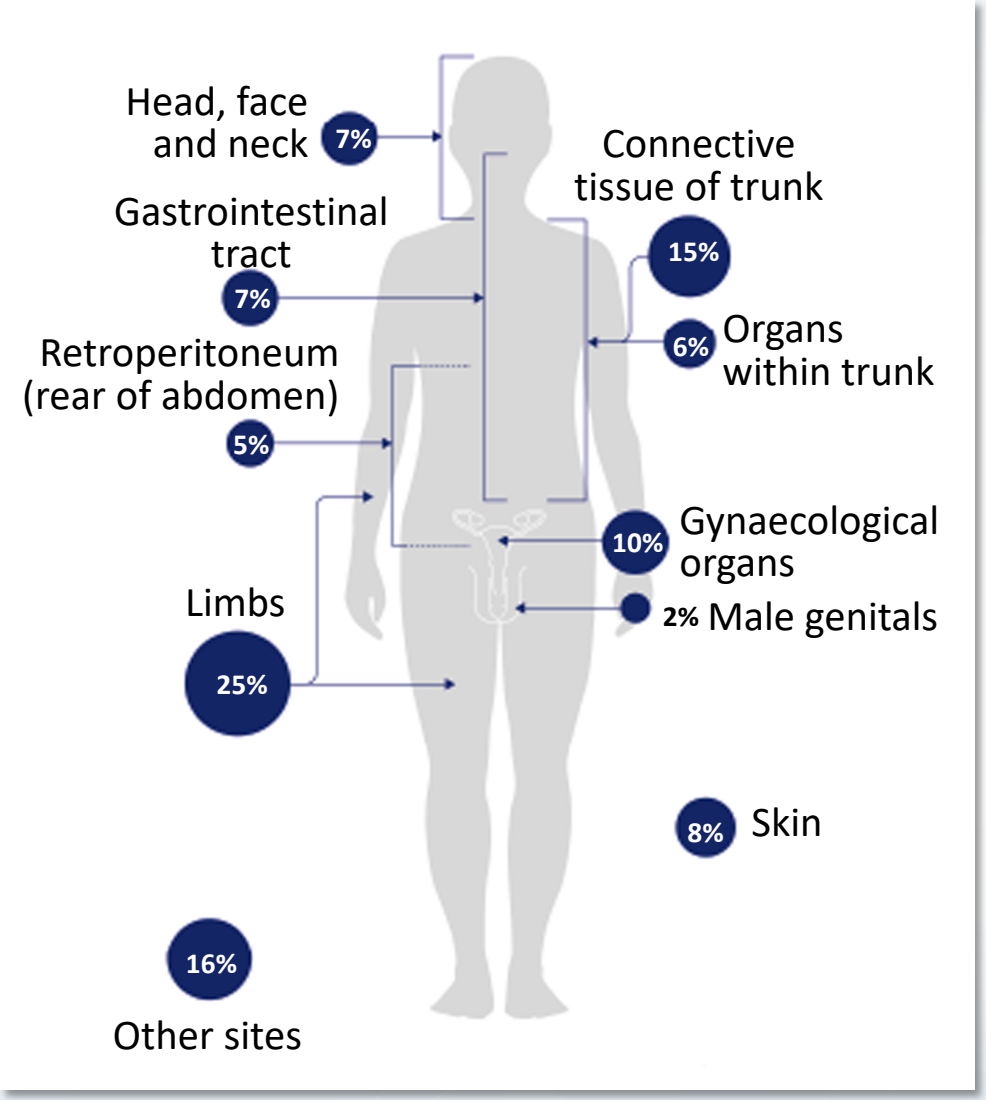
- Three general groups:
  - Soft tissue sarcomas
  - Bone sarcomas



GIST is a soft tissue sarcoma with a unique paradigm of care

Pollack S. Personal communication

STS Distribution by Anatomical Site



- May present virtually anywhere in the body
- Majority occur in the extremities but also affect the retroperitoneum, chest wall, head and neck and subcutaneous tissues
- Arise from muscle, adipose, fibrous, cartilage, nerve or vascular tissue

https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/soft-tissue-sarcoma/incidence#heading-Three

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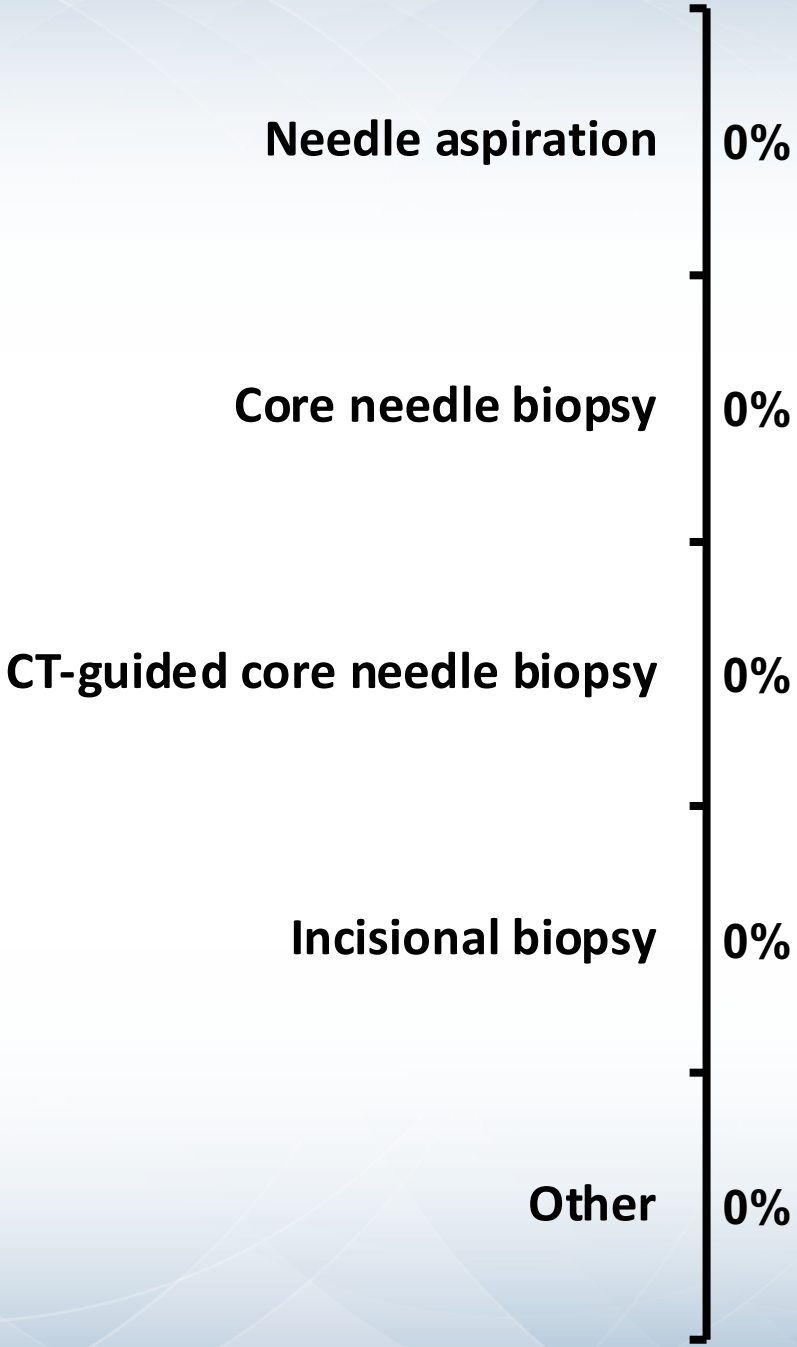
A 35-year-old patient presents with a softball-sized mass (8 centimeters) deep in the tissue of her right thigh that has increased in size over the past 4 months and is causing discomfort. The patient does not have a family history of cancer. What type of biopsy should be done on the mass?

1. Needle aspiration
2. Core needle biopsy
3. CT-guided core needle biopsy
4. Incisional biopsy
5. Other



A 35-year-old patient presents with a softball-sized mass (8 centimeters) deep in the tissue of her right thigh that has increased in size over the past 4 months and is causing discomfort. The patient does not have a family history of cancer. What type of biopsy should be done on the mass?

 MARK AGULNIK, MD	CT-guided core needle biopsy
 KRISTEN GANJOO, MD	Core needle biopsy
 SUZANNE GEORGE, MD	CT-guided core needle biopsy
 SHREYASKUMAR PATEL, MD	CT-guided core needle biopsy
 SETH M POLLACK, MD	CT-guided core needle biopsy
 RICHARD F RIEDEL, MD	CT-guided core needle biopsy
 BRIAN A VAN TINE, MD, PHD	CT-guided core needle biopsy
 VICTOR M VILLALOBOS, MD, PHD	Core needle biopsy

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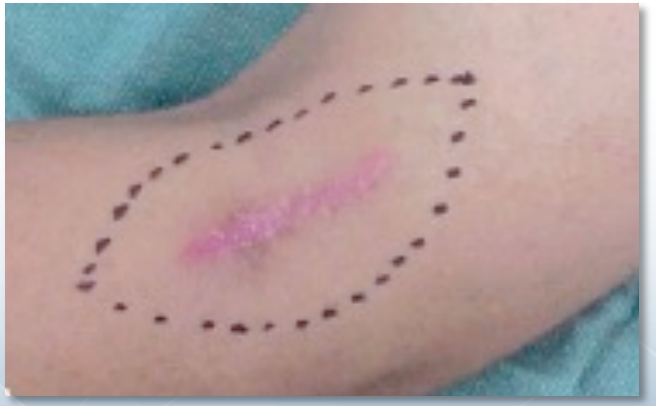
A patient presents with a mass: Do they need a biopsy?

- Biopsy
  - Any soft tissue mass that is enlarging
  - Any mass that is larger than 5 centimeters
  - Any mass that is symptomatic
  - Any new mass (>3 cm) that is persisting beyond 4 weeks
- However, when imaging suggests intra-abdominal or retroperitoneal sarcoma, biopsy is not helpful unless
  - Lymphoma or germ-cell tumor is suspected
  - Preoperative chemotherapy and/or radiation therapy is planned
  - Tumor is unresectable

Lewis J, Brennan MF. *Current Probl Surg* 1996;33:817.
Mankin HJ et al. *J Bone Joint Surg* 1996;78A:656-63.
Pollack S. Personal communication

Biopsy

- Usually core biopsy or incisional biopsy preferred
  - Extremity masses should be biopsied through a small *longitudinal* incision so that entire biopsy tract can be excised at the time of resection.
- Tru-Cut® core biopsies may be adequate.
- FNA has no role in initial diagnosis of extremity STS. May document a recurrence.
- Excisional biopsy for small (<3 cm) superficial tumors.



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Should every patient with a diagnosis of soft tissue sarcoma have his/her slides reviewed by an expert pathologist? Should every patient be evaluated, either in person or through virtual communication, by a center of excellence for sarcoma?

	Expert pathologist	Center of excellence
 MARK AGULNIK, MD	Yes	Yes
 KRISTEN GANJOO, MD	Yes	Yes
 SUZANNE GEORGE, MD	Yes	Yes
 SHREYASKUMAR PATEL, MD	Yes	Yes
 SETH M POLLACK, MD	Yes	Yes
 RICHARD F RIEDEL, MD	Yes	Yes
 BRIAN A VAN TINE, MD, PHD	Yes	Yes
 VICTOR M VILLALOBOS, MD, PHD	Yes	Yes

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Histological Subtype

- Presant and colleagues reviewed 216 sarcoma cases to see if experienced academic pathologists would agree with pathologists who see few sarcomas.
- Experienced pathologists have a high degree of concordance.
- However, inexperienced pathologists misclassify sarcomas 27% of the time.
- 6% of tumors initially called “sarcomas” were not actually sarcomas.
- **Summary: any pathology thought to be sarcoma should be reviewed by an experienced bone and soft tissue pathologist.**

Presant et al. *JCO* 1986
Pollack S. Personal communication

Histological Grade

- Histological grade predicts risk of metastasis and survival
- FNLCC (most common): Based on differentiation, mitosis, necrosis. Slight improvement in predictive power over histology-based NCI system.
- Grade is of no prognostic value in certain subtypes:
  - MPNST
  - Extraskeletal myxoid chondrosarcoma
- Others are always considered high grade
  - Angiosarcoma
  - PNET

Guillon, *JCO* 1997
Coindre, *Arch Pathol Lab Med* 2006
Pollack S. Personal communication

The local hospital diagnosis for the 35-year-old patient is Grade 3 undifferentiated pleomorphic sarcoma (UPS). What type of imaging of the mass is optimal? What imaging studies should be done to stage this patient?

	Imaging mass	Imaging for staging
 MARK AGULNIK, MD	MRI	CT chest/abdomen/pelvis
 KRISTEN GANJOO, MD	MRI	CT chest/abdomen/pelvis; bone scan
 SUZANNE GEORGE, MD	MRI	CT chest/abdomen/pelvis
 SHREYASKUMAR PATEL, MD	MRI	CT chest
 SETH M POLLACK, MD	MRI	Chest PET-CT (no contrast)
 RICHARD F RIEDEL, MD	MRI	CT chest
 BRIAN A VAN TINE, MD, PHD	MRI	CT chest/abdomen/pelvis
 VICTOR M VILLALOBOS, MD, PHD	MRI	CT chest/abdomen/pelvis

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Imaging

MRI:

- Important for sarcomas of extremities, head and neck, chest wall
- Distinguishes tumor from adjacent muscle and fat
- Accurate at defining tumor size, relationship to muscle compartments, fascial planes, bones and neurovascular bundles

CT:

- Initial chest CT recommended to evaluate for metastatic disease in all patients with sarcoma
- Used as main evaluation for primary sarcomas in the abdomen and pelvis

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Prognostic Factors for Survival

Histologic grade (most important)

- Differentiation (histology specific), mitotic rate, extent of necrosis

Tumor size

Pathologic stage

Other tumor-related factors

- Depth (superficial/deep to fascia)
- Site (extremity vs trunk/retroperitoneum; distal vs proximal)

Treatment setting

- Outcomes improved at high-volume sarcoma treatment centers
  - Improved R0 margin rate, local recurrence rate, 30-day mortality, overall survival and functional outcomes

Adherence to guidelines — associated with improved survival

Abarca T et al. *J Surg Oncol* 2018;117:1479; Bagaria SP et al. *Sarcoma* 2018a, b; Gutierrez JC et al. *Ann Surg* 2007;245:952; Clasby R et al. *Br J Surg* 1997;84(12):1692; Gustafson. *Acta Orthop Scand* 1994;65(1):47; Voss RK et al. *Ann Surg Oncol* 2017;24(11):3271.

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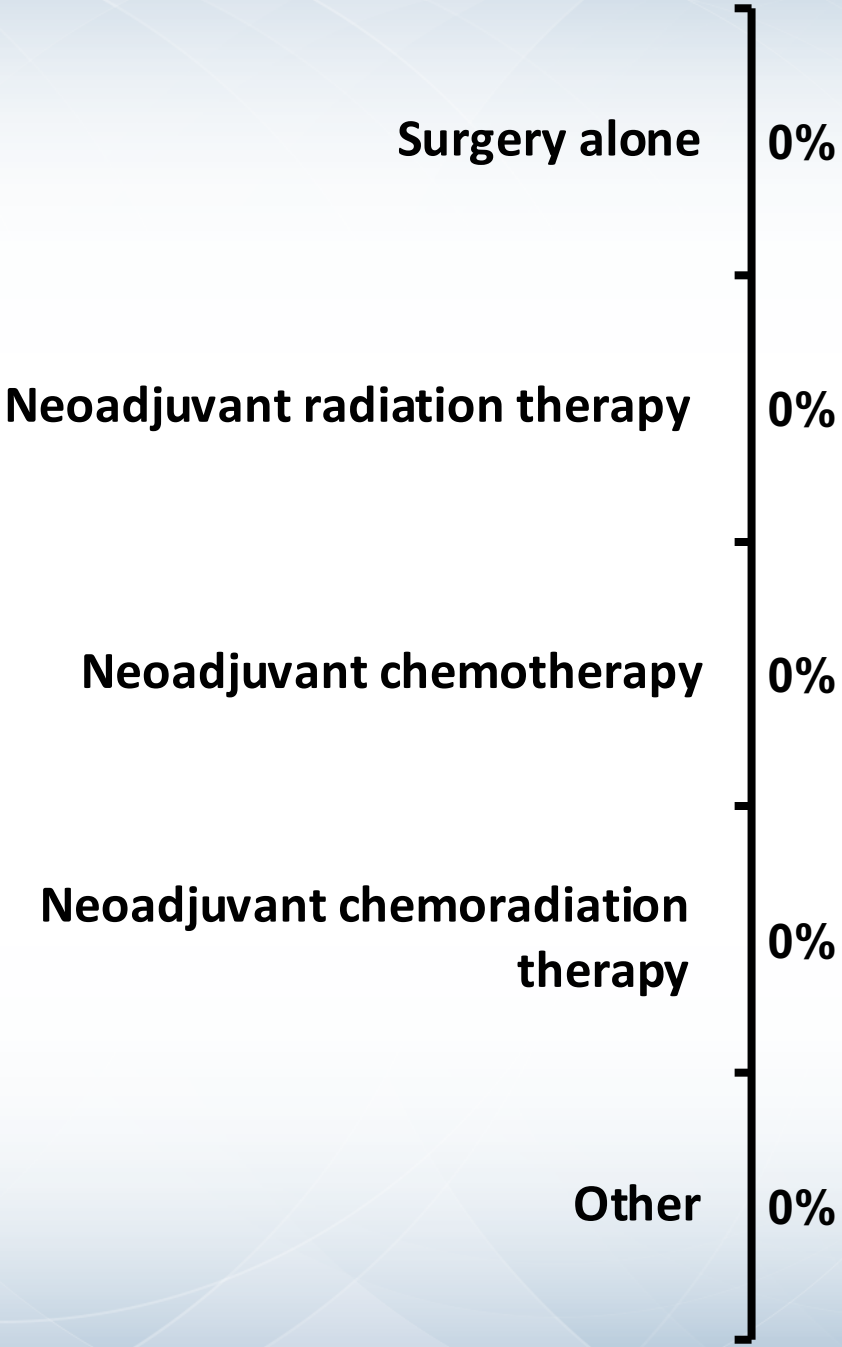
Biopsy of the tumor of the 35-year-old patient reveals a 3-cm Grade 3 undifferentiated pleomorphic sarcoma (UPS). Metastatic workup (CT of the chest and abdomen) is negative. In general, what would be your initial management approach?

1. **Surgery alone**
2. **Neoadjuvant radiation therapy**
3. **Neoadjuvant chemotherapy**
4. **Neoadjuvant chemoradiation therapy**
5. **Other**



Biopsy of the tumor of the 35-year-old patient reveals Grade 3 UPS. Metastatic workup (CT of the chest and abdomen) is negative. In general, what would be your initial management approach if the primary tumor were…

	3 centimeters	8 centimeters
 MARK AGULNIK, MD	Surgery alone	Neoadjuvant RT → surgery ***OR*** surgery
 KRISTEN GANJOO, MD	Surgery alone	Neoadjuvant RT → surgery
 SUZANNE GEORGE, MD	Likely neoadjuvant RT → surgery	Neoadjuvant RT → surgery
 SHREYASKUMAR PATEL, MD	Surgery +/- neo(adjuvant) RT	Neoadjuvant chemo → neoadjuvant RT → surgery
 SETH M POLLACK, MD	Neoadjuvant RT → surgery	Neoadjuvant chemo → neoadjuvant RT → surgery
 RICHARD F RIEDEL, MD	Neoadjuvant RT → surgery	Neoadjuvant RT → surgery
 BRIAN A VAN TINE, MD, PHD	Surgery alone	Surgery +/- neo(adjuvant) RT
 VICTOR M VILLALOBOS, MD, PHD	Surgery alone (if wide negative margins possible)	Neoadjuvant chemo → neoadjuvant RT → surgery

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Multimodality Treatment of Localized STS of the Extremities and Chest Wall

Individualized treatment due to variety of anatomic sites, histologies, grade and tumor size

Surgery + radiation therapy (RT) for most

- Surgery alone for <5 cm, low grade, superficial?

Neoadjuvant chemoRT

- Limited data, optimal approach not defined
- May be beneficial for larger, higher-grade tumors when radical resection would compromise function

Neoadjuvant chemotherapy +/- hyperthermia

- Role in large, locally advanced STS?

Adjuvant chemotherapy

- Controversial — guidelines regard it as an option in individual cases, particularly high-risk disease when toxicities are discussed with patient

Casali PG et al; ESMO Guidelines Committee and EURACAN. *Ann Oncol* 2018;29(Suppl 4):51-67. NCCN Soft Tissue Sarcoma, v2.2018.

Extremity STS: Surgery

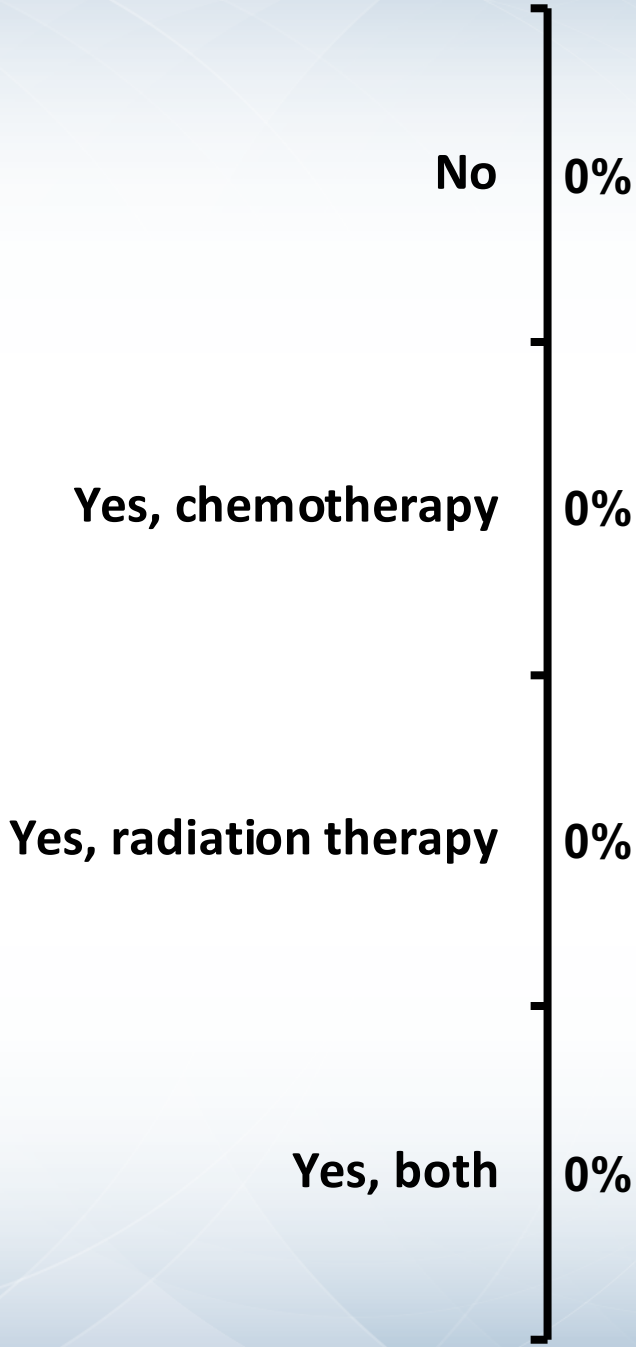
- Surgical excision is the dominant modality of curative therapy:
  - Whenever possible, function- and limb-sparing procedures should be performed
  - As long as the entire tumor is removed, less radical procedures do not adversely affect local recurrence or outcome
  - Goal is complete removal of the tumor with negative (2- to 3-cm) margins and maximal preservation of function

Rosenberg SA, Tepper J et al. *Ann Surg* 196;305-15:1982

Pollack S. Personal communication

If the 35-year-old patient with an 8-cm Grade 3 UPS initially underwent surgery and had an R0 resection, would you recommend adjuvant chemotherapy or radiation therapy?

1. No
2. Yes, chemotherapy
3. Yes, radiation therapy
4. Yes, both



If the 35-year-old patient with Grade 3 UPS initially underwent surgery and had an R0 resection, would you recommend adjuvant chemotherapy or radiation therapy if the primary tumor were…

	3 centimeters		8 centimeters	
	Chemotherapy	Radiation therapy	Chemotherapy	Radiation therapy
 MARK AGULNIK, MD	No	No	Dox/ifos	Yes
 KRISTEN GANJOO, MD	No	No	Dox/ifos	Yes
 SUZANNE GEORGE, MD	No	Probably	No	Yes
 SHREYASKUMAR PATEL, MD	No	Depends	Dox/ifos	Yes
 SETH M POLLACK, MD	No	Yes	No	Yes
 RICHARD F RIEDEL, MD	No	Depends	No	Yes
 BRIAN A VAN TINE, MD, PHD	No	No	No	Yes
 VICTOR M VILLALOBOS, MD, PHD	No	No	Dox/ifos	Yes

Dox/ifos = doxorubicin/ifosfamide

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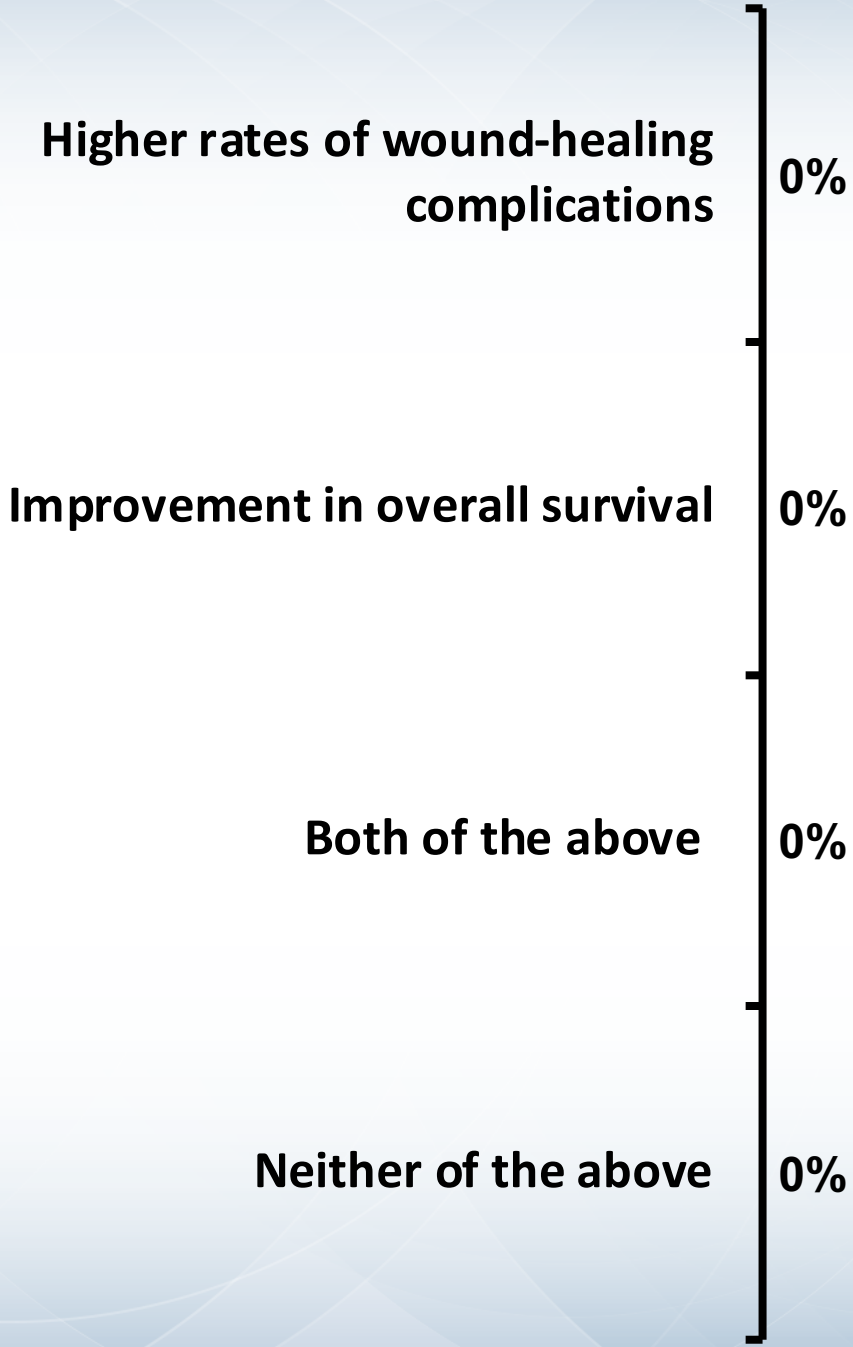
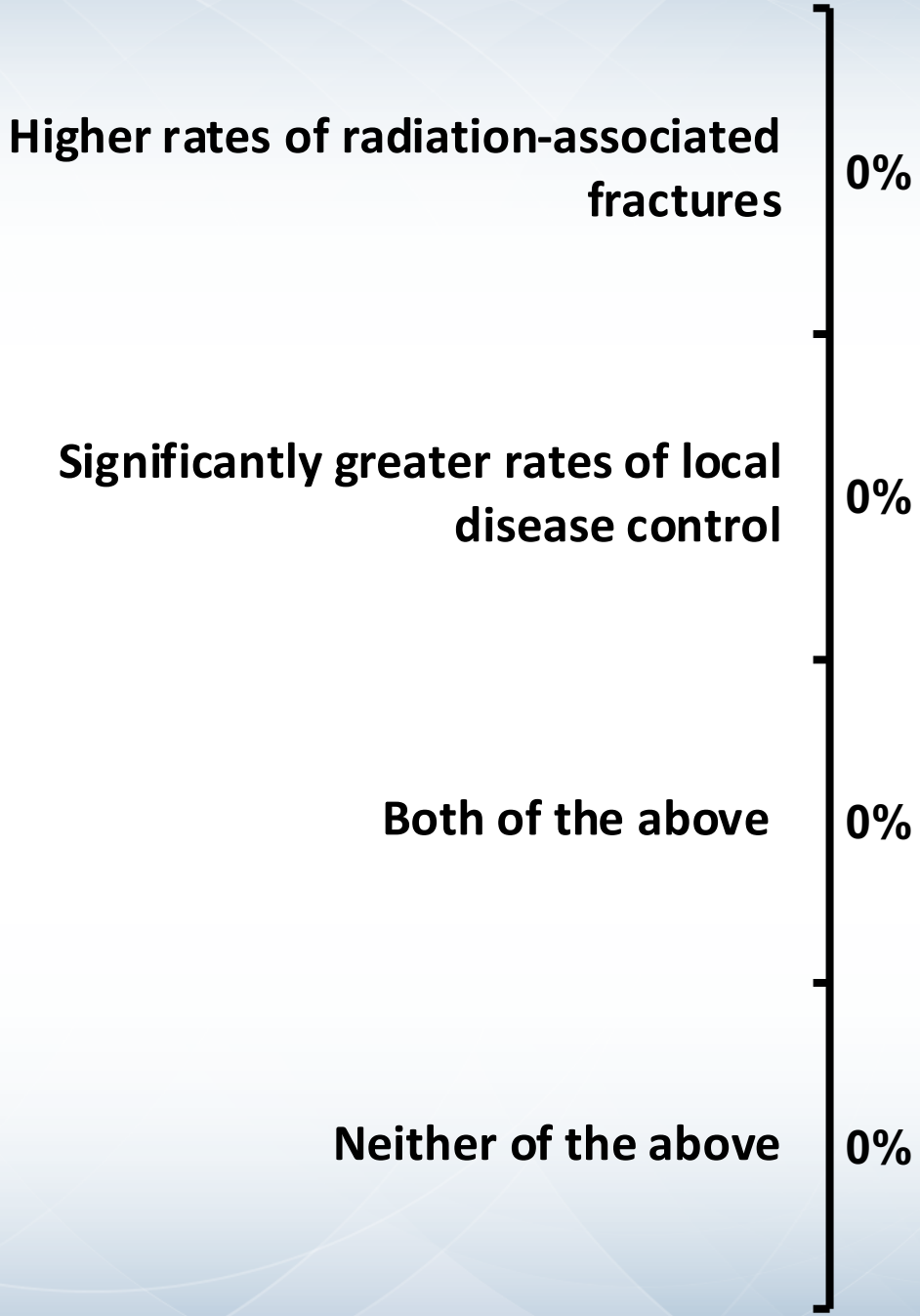
Neoadjuvant radiation therapy is associated with which of the following compared to adjuvant radiation therapy among patients with localized soft tissue sarcomas of the extremities?

1. Higher rates of wound-healing complications
2. Improvement in overall survival
3. Both of the above
4. Neither of the above

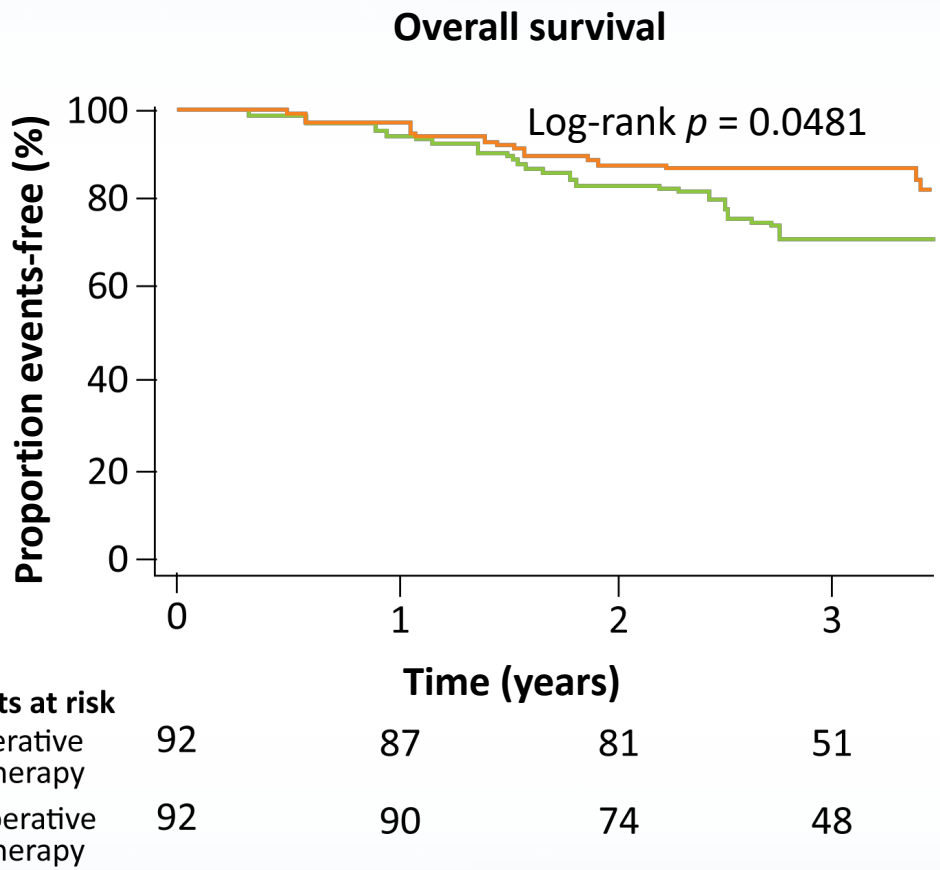


Adjuvant radiation therapy is associated with which of the following compared to neoadjuvant radiation therapy among patients with localized soft tissue sarcomas of the extremities?

1. Higher rates of radiation-associated fractures
2. Significantly greater rates of local disease control
3. Both of the above
4. Neither of the above



Adjuvant versus Neoadjuvant Radiation



Although the O'Sullivan series showed better survival with neoadjuvant rads compared with postop rads, others have criticized it as it was not an intention-to-treat analysis.

Neoadjuvant Radiation:
Higher rates of wound complications
Higher rates of returning to the operating room

Adjuvant Radiation:
Higher rates of edema and fibrosis
Higher rates of radiation-associated fractures

Advantages/disadvantages to both. Both are considered acceptable practices.

O'Sullivan et al, *Lancet* 2002
Pollack S. Personal communication

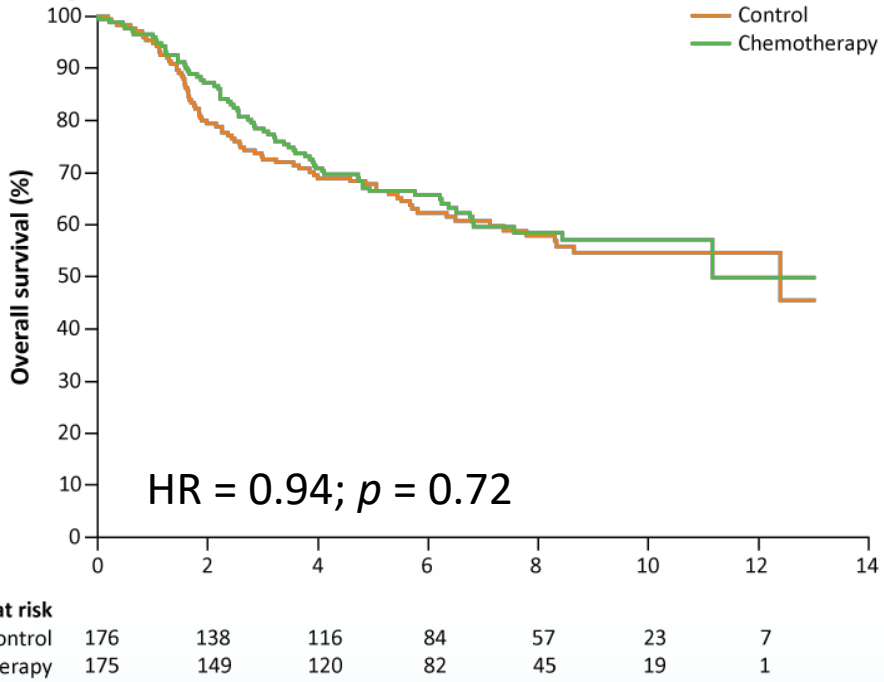
Role of Adjuvant Chemotherapy

- No consensus on the role of adjuvant chemotherapy (CT)
  - Individual studies are underpowered, with broad range of drug dosages, mixed histologies, nonuniform grade of disease
  - Meta-analysis of 18 randomized controlled trials of adjuvant CT for patients with localized, resectable STS suggests benefit for local and distant recurrence and overall survival, particularly with doxorubicin/ifosfamide[1]
  - Pooled analysis of 2 large adjuvant trials comparing doxorubicin-based CT to observation only for completely resected STS demonstrated that adjuvant CT is **not** associated with better OS[2]
  - Applicability of adjuvant CT to nonextremity STS is uncertain

[1] Pervaiz N et al. *Cancer* 2008;113(3):573-81. [2] Le Cesne A et al. *Ann Oncol* 2014;25:2425-32.

EORTC 62931: Adjuvant Chemotherapy with Doxorubicin/Ifosfamide/Lenograstim for Resected STS (N = 351)

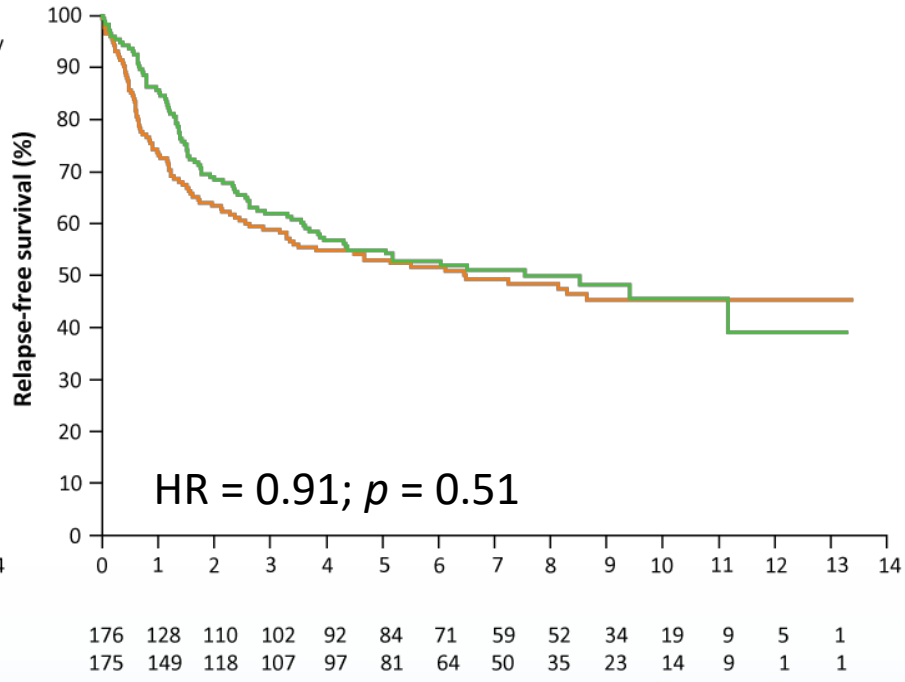
Overall survival



Number at risk

Control	176	138	116	84	57	23	7
Chemotherapy	175	149	120	82	45	19	1

Relapse-free survival



176	128	110	102	92	84	71	59	52	34	19	9	5	1
175	149	118	107	97	81	64	50	35	23	14	9	1	1

Woll PJ et al. *Lancet Oncol* 2012;13(10):1045-54.

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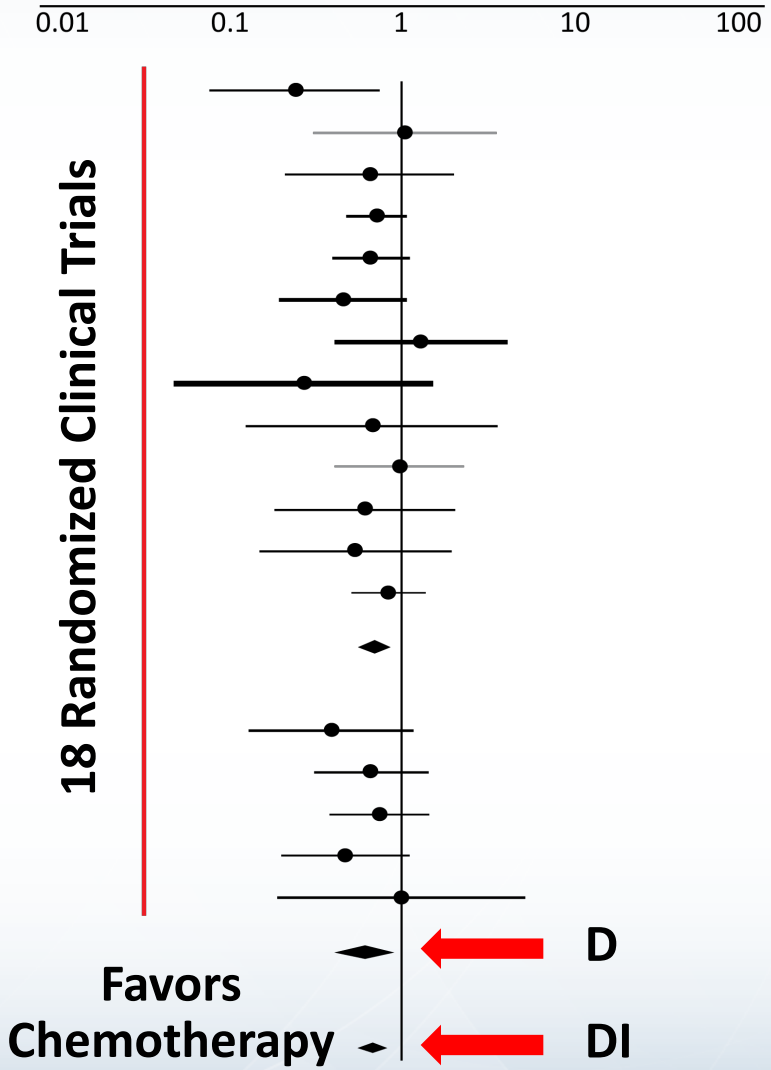
EORTC 62931: Adjuvant Chemotherapy with Doxorubicin/Ifosfamide/Lenograstim for Resected STS (N = 351)

- Trend toward OS and RFS benefit from chemotherapy for patients with large, high-grade and extremity STS
- Limitations
  - Low-dose ifosfamide (5 g/m^2)
  - Accrual took approximately 9 years (first patient 1995)
  - More than 50% of patients had intermediate- or low-grade disease
  - More than one third of patients had disease not in the extremities
  - More than one third of patients had unknown specific histology
  - Included small tumors (size range 0.3 cm-38 cm)
  - 18% of deaths not sarcoma related

Woll PJ et al. *Lancet Oncol* 2012;13(10):1045-54; Trent JC. ASCO 2018.

Meta-analysis of Adjuvant Chemotherapy for Localized, Resectable STS (N = 1,953)



- STS with resection +/- radiation
- Large sample size
- Doxorubicin (50-90 mg/m^2) +/- ifosfamide (5-9 g/m^2)
- OS (11%) and RFS (12%) benefit from chemotherapy (D + I)

Limitations

- Broad dose range for doxorubicin and ifosfamide
- Included intermediate and low grade
- Included any STS histologic subtype (chemoresistant? GIST?)
- No subset analysis by anatomic site, grade, size, histology
- Unreported disease-specific survival

Pervaiz N et al. *Cancer* 2008;113(3):573-81. Trent JC. ASCO 2018

Meta-analysis of Randomized Controlled Trials of Adjuvant Chemotherapy for Localized, Resectable STS

Absolute Risk Reduction with Adjuvant Chemotherapy

Regimen	Local recurrence	Distant recurrence	Any recurrence	Survival
Doxorubicin	3% (1%-7%)	9% (4%-14%)	9% (4%-14%)	5% (6%-21%)
Doxorubicin + ifosfamide	**5% (1%-12%)**	**10% (1%-19%)**	**12% (3%-21%)**	**11% (3%-19%)**
Doxorubicin or doxorubicin + ifosfamide	4% (0%-7%)	9% (5%-14%)	10% (5%-15%)	6% (2%-11%)

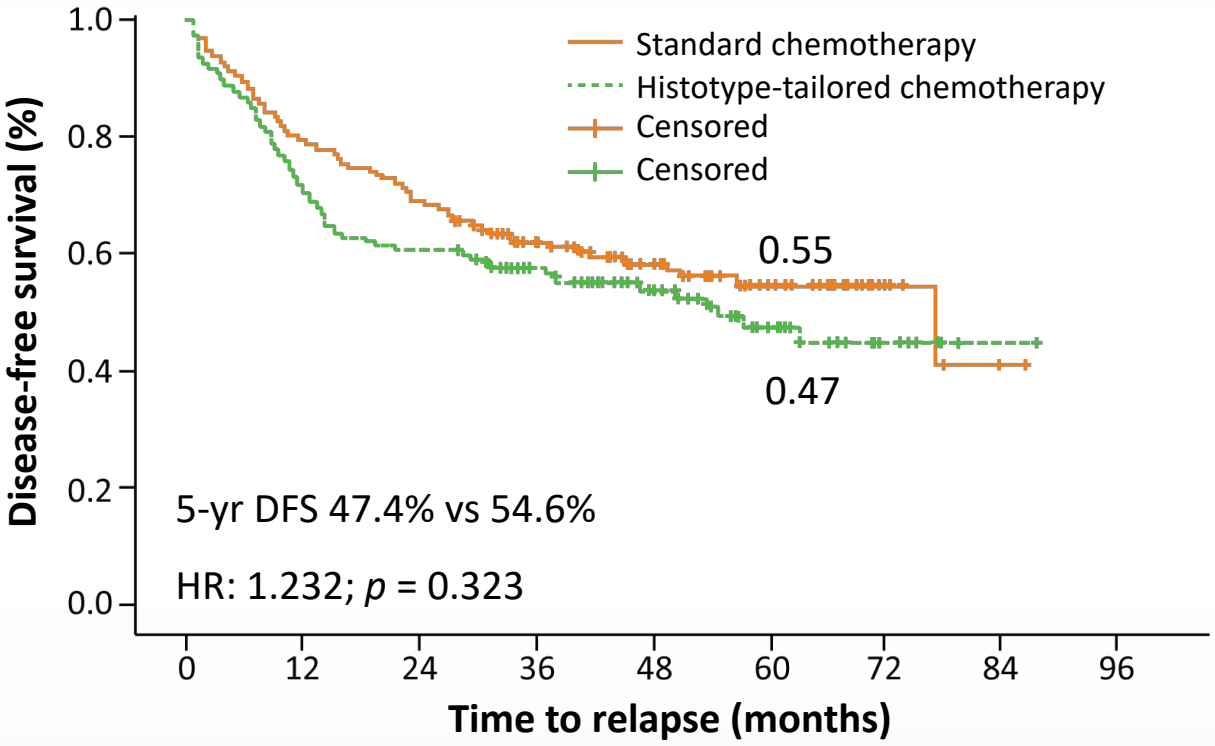
Pervaiz N et al. *Cancer* 2008;113(3):573-81.

Objectives of Neoadjuvant Chemotherapy

- Decrease local recurrence rate
- Eradicate microscopic metastases
- Improve survival
- **Alleviate tumor-related pain**
- **Downstage unresectable tumor to enable resection**
- **Determine individual tumor chemosensitivity**

Trent JC. ASCO 2018.

Final Results of a Phase III Trial of Histology-Tailored Neoadjuvant Chemotherapy versus Standard Chemotherapy for High-Risk STS (N = 287)



- Epirubicin + ifosfamide x 3 cycles OR histology-tailored therapy x 3 cycles
  - Synovial sarcoma: High-dose ifosfamide
  - High-grade myxoid liposarcoma: Trabectedin
  - Leiomyosarcoma: Gemcitabine + dacarbazine
  - Malignant peripheral nerve sheath tumor: Ifosfamide + etoposide
  - Unclassified pleomorphic sarcoma: Gemcitabine + docetaxel

- 5-year overall survival (histology-tailored therapy versus epirubicin + ifosfamide):
  - 65.9% versus 75.7% (HR 1.766, $p = 0.018$)

Gronchi A et al. ASCO 2019;Abstract 11000.

A 35-year-old woman presents with a softball-sized mass deep in the tissue of her right thigh that has increased in size over the past 18 months. It is now difficult for her to cross her legs, and she is experiencing pain. Initial imaging studies and biopsy reveal a Grade 1 leiomyosarcoma (LMS). She does not have a family history of cancer. In general, what would be your initial management approach if the primary tumor were…

	3 centimeters	8 centimeters
 MARK AGULNIK, MD	Surgery alone	Neoadjuvant RT → surgery *OR* surgery
 KRISTEN GANJOO, MD	Surgery alone	Surgery alone
 SUZANNE GEORGE, MD	Possibly neoadjuvant RT → surgery	Neoadjuvant RT → surgery
 SHREYASKUMAR PATEL, MD	Surgery alone	Surgery alone
 SETH M POLLACK, MD	Surgery alone (if surgeon confident of wide margins)	Neoadjuvant RT → surgery
 RICHARD F RIEDEL, MD	Surgery alone	Neoadjuvant RT → surgery
 BRIAN A VAN TINE, MD, PHD	Surgery alone	Surgery alone (RT if positive margins, re-excision not possible)
 VICTOR M VILLALOBOS, MD, PHD	Surgery (reassess tumor biology)	Surgery alone (if wide negative margins possible)

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If the 35-year-old patient with Grade 1 LMS initially underwent surgery and had an R0 resection, would you recommend adjuvant chemotherapy or radiation therapy if the primary tumor were…

	3 centimeters		8 centimeters	
	Chemotherapy	Radiation therapy	Chemotherapy	Radiation therapy
 MARK AGULNIK, MD	No	No	No	Yes
 KRISTEN GANJOO, MD	No	No	No	No
 SUZANNE GEORGE, MD	No	No	No	Yes
 SHREYASKUMAR PATEL, MD	No	No	No	Yes
 SETH M POLLACK, MD	No	No	No	No
 RICHARD F RIEDEL, MD	No	No	No	No
 BRIAN A VAN TINE, MD, PHD	No	No	No	No
 VICTOR M VILLALOBOS, MD, PHD	No	No	No	Possibly

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Management of Soft Tissue Sarcoma (STS)

MODULE 1: Overview of STS; Initial Workup and Classification

- Incidence, biology and histopathologic classification
- Biopsy technique; imaging workup
- Indications for involvement of specialized tertiary care providers

MODULE 2: Management of Localized Disease

- Role of neoadjuvant/adjuvant radiation therapy
- Role of neoadjuvant/adjuvant chemotherapy

MODULE 3: Management of Metastatic STS

- Local treatment of oligometastatic disease
- Selection and sequencing of systemic treatments
- Investigational strategies and agents

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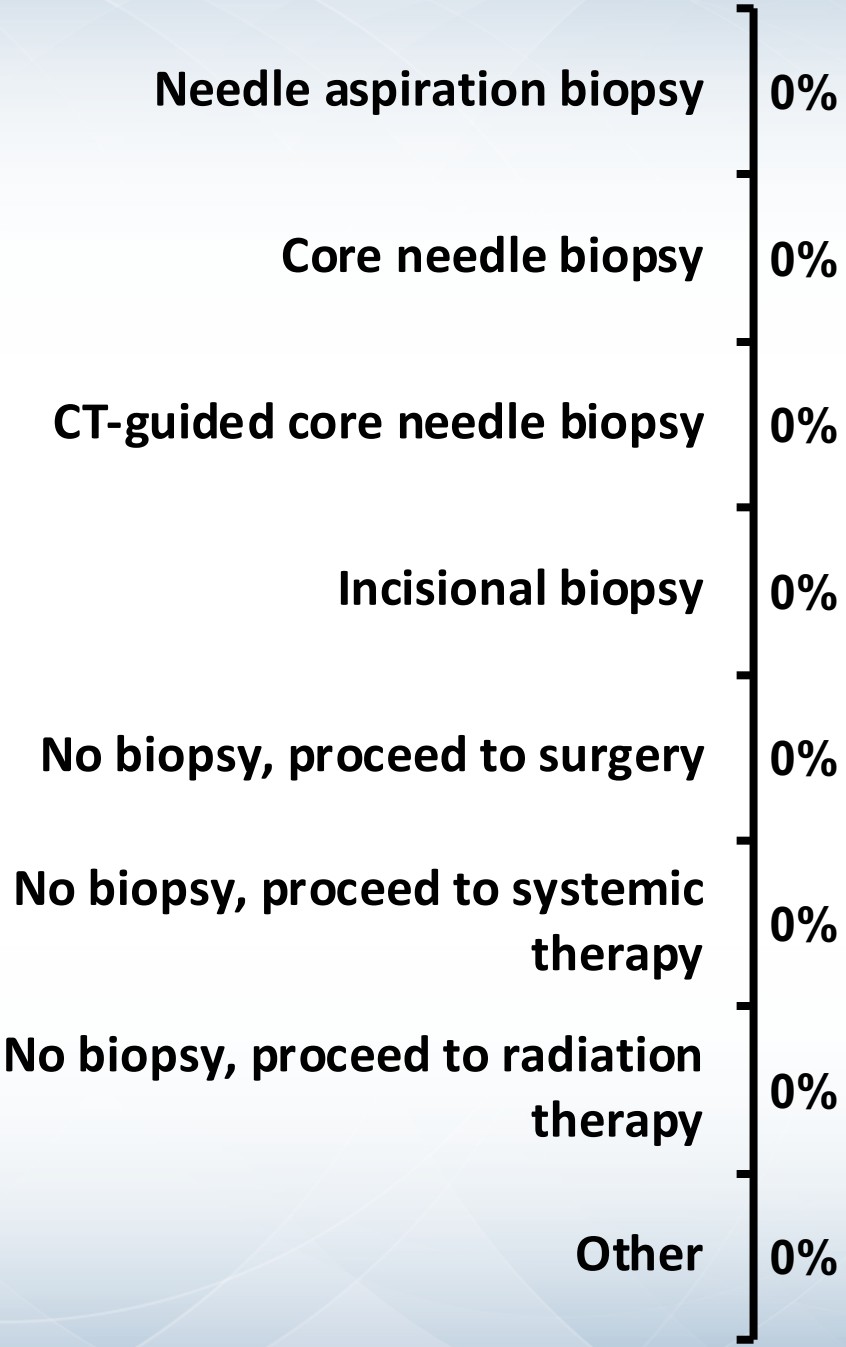
A 35-year-old patient diagnosed with an 8-cm, Grade 3 UPS of the right thigh undergoes resection followed by radiation therapy but no adjuvant chemotherapy. One year after completion of therapy, follow-up imaging reveals two 1.5-cm lesions in the left lower lobe of the lung. No other site of disease is detected. The patient is asymptomatic. What would be your initial approach?

1. Needle aspiration biopsy
2. Core needle biopsy
3. CT-guided core needle biopsy
4. Incisional biopsy
5. No biopsy, proceed to surgery
6. No biopsy, proceed to systemic therapy
7. No biopsy, proceed to radiation therapy
8. Other



A 35-year-old patient diagnosed with an 8-cm, Grade 3 UPS of the right thigh undergoes resection followed by radiation therapy but no adjuvant chemotherapy. One year after completion of therapy, follow-up imaging reveals two 1.5-cm lesions in the left lower lobe of the lung. No other site of disease is detected. The patient is asymptomatic. What type of biopsy should be done on the mass?

What type of biopsy should be done if the primary tumor were a Grade 1 LMS?

	Grade 3 UPS	Grade 1 LMS
 MARK AGULNIK, MD	CT-guided core needle biopsy	CT-guided core needle biopsy
 KRISTEN GANJOO, MD	Needle aspiration	Needle aspiration
 SUZANNE GEORGE, MD	None, proceed to surgery or RT	None, proceed to surgery
 SHREYASKUMAR PATEL, MD	None, proceed to systemic therapy	CT-guided core needle biopsy
 SETH M POLLACK, MD	None *OR* CT-guided core needle biopsy	None *OR* CT-guided core needle biopsy
 RICHARD F RIEDEL, MD	CT-guided core needle biopsy	CT-guided core needle biopsy
 BRIAN A VAN TINE, MD, PHD	CT-guided core needle biopsy	CT-guided core needle biopsy
 VICTOR M VILLALOBOS, MD, PHD	None, proceed to systemic therapy	CT-guided core needle biopsy

For which sites of metastatic disease have you sent patients for surgical resection?

 MARK AGULNIK, MD	Lung, liver, thyroid, brain
 KRISTEN GANJOO, MD	Lung, liver
 SUZANNE GEORGE, MD	Many different sites
 SHREYASKUMAR PATEL, MD	Any resectable site as long as the DFI is long (>12 months) and site is amenable to resection
 SETH M POLLACK, MD	Lung, liver, isolated intra-abdominal mets from a retroperitoneal tumor
 RICHARD F RIEDEL, MD	Lungs, liver, peritoneal cavity, brain
 BRIAN A VAN TINE, MD, PHD	Lung, liver, bone
 VICTOR M VILLALOBOS, MD, PHD	Liver, lung, peritoneal cavity, extremities

Research To Practice®

Management of Soft Tissue Sarcoma (STS)

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Selection and Sequencing of Systemic Treatments – Clinical Scenarios

Undifferentiated Pleomorphic Sarcoma

- 35-year-old with asymptomatic, low-volume disease
- 35-year-old with symptomatic, larger-volume disease (no visceral involvement)
- 75-year-old with asymptomatic, low-volume disease
- 75-year-old with symptomatic, larger-volume disease (no visceral involvement)

Leiomyosarcoma

- 35-year-old with asymptomatic, low-volume disease
- 35-year-old with symptomatic, larger-volume disease (no visceral involvement)

Systemic Treatments with Activity in STS

Combination Regimens

- AD (doxorubicin/dacarbazine)
- AIM (doxorubicin/ifosfamide/mesna)
- MAID (mesna/doxorubicin/ifosfamide/dacarbazine)
- Ifosfamide/epirubicin/mesna
- Gemcitabine/docetaxel
- Gemcitabine/vinorelbine
- Gemcitabine/dacarbazine
- Doxorubicin/olaratumab

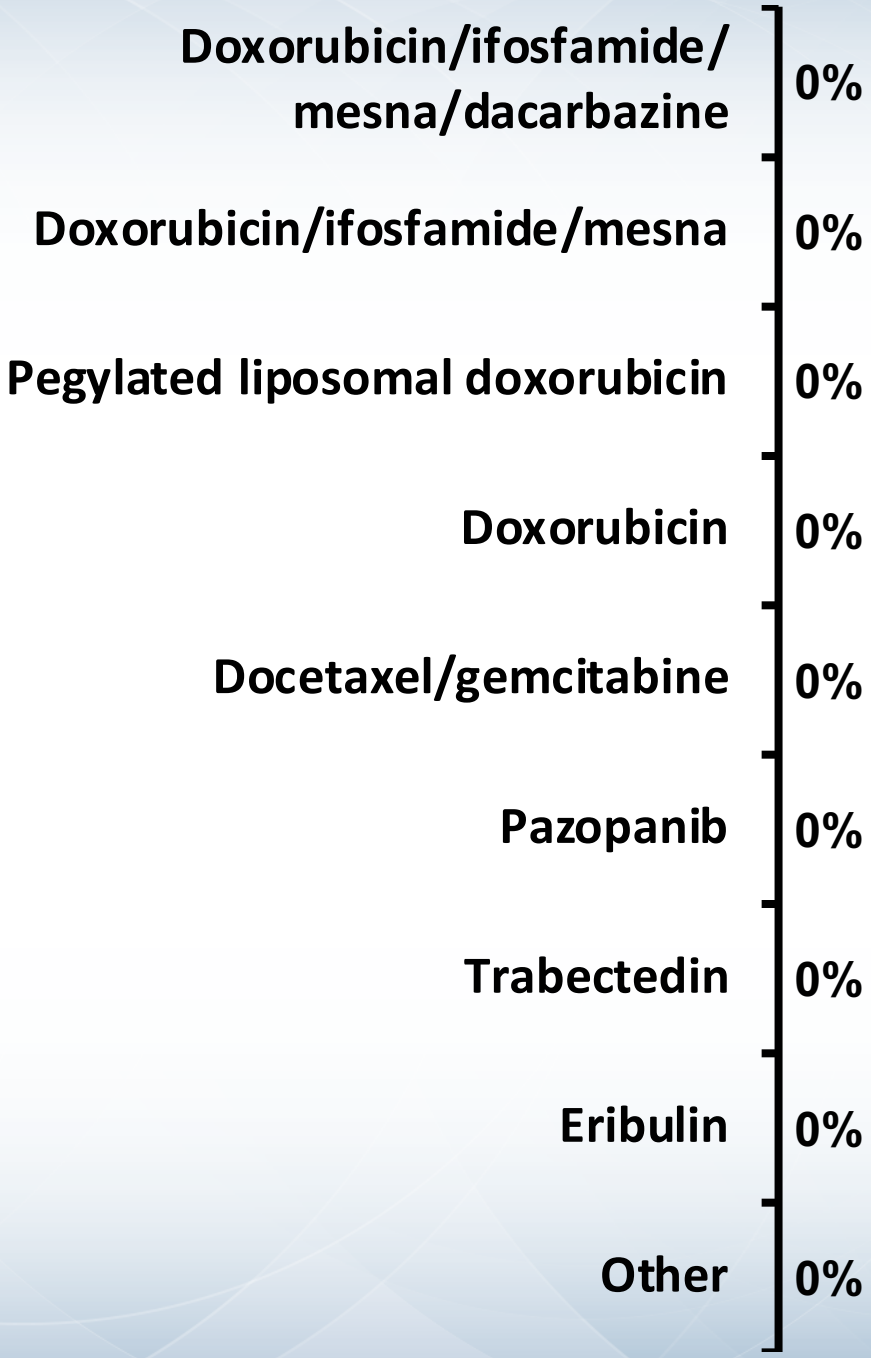
Single Agents

- Doxorubicin
- Ifosfamide
- Epirubicin
- Gemcitabine
- Dacarbazine
- Liposomal doxorubicin
- Temozolomide
- Vinorelbine
- Eribulin
- Trabectedin
- Pazopanib

NCCN Soft Tissue Sarcoma, v1.2019.

What would be your most likely first-line therapy for a 35-year-old patient who underwent resection of a localized undifferentiated pleomorphic sarcoma followed by radiation therapy but no adjuvant chemotherapy and now presents with low-volume, asymptomatic metastatic disease?

1. Doxorubicin/ifosfamide/mesna/dacarbazine
2. Doxorubicin/ifosfamide/mesna
3. Pegylated liposomal doxorubicin
4. Doxorubicin
5. Docetaxel/gemcitabine
6. Pazopanib
7. Trabectedin
8. Eribulin
9. Other



What would be your most likely sequence of therapies for a 35-year-old patient who underwent resection of a localized undifferentiated pleomorphic sarcoma followed by radiation therapy but no adjuvant chemotherapy and now presents with low-volume, asymptomatic metastatic disease?

	First line	Second line	Third line
 MARK AGULNIK, MD	Doxorubicin	Gem/docetaxel	Pazopanib
 KRISTEN GANJOO, MD	Doxorubicin	Gem/docetaxel	Pazopanib
 SUZANNE GEORGE, MD	Doxorubicin	Gem/docetaxel	Pazopanib
 SHREYASKUMAR PATEL, MD	Dox/ifos	Gem/docetaxel	Pazopanib
 SETH M POLLACK, MD	Doxorubicin	Gem/docetaxel	Pazopanib
 RICHARD F RIEDEL, MD	Doxorubicin	Gem/docetaxel	Dacarbazine
 BRIAN A VAN TINE, MD, PHD	Doxorubicin	Gem/docetaxel	Pazopanib
 VICTOR M VILLALOBOS, MD, PHD	Doxorubicin	Gem/docetaxel	Pazopanib

Gem = gemcitabine; dox/ifos = doxorubicin/ifosfamide

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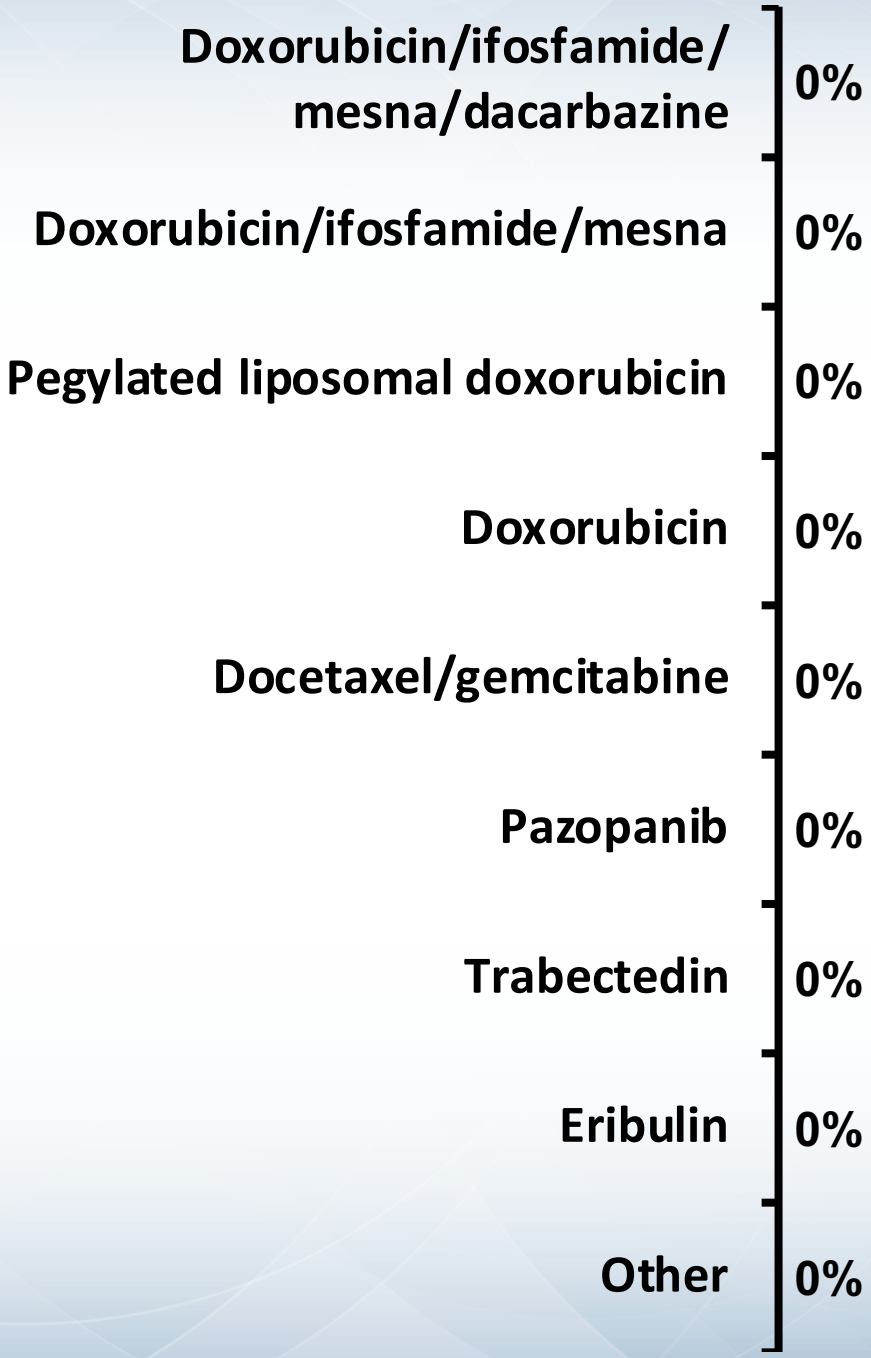
What would be your most likely first-line therapy for a 35-year-old patient who underwent resection of a localized undifferentiated pleomorphic sarcoma followed by radiation therapy but no adjuvant chemotherapy and now presents with larger-volume, symptomatic metastatic disease with no visceral involvement?

1. Doxorubicin/ifosfamide/mesna/dacarbazine
2. Doxorubicin/ifosfamide/mesna
3. Pegylated liposomal doxorubicin
4. Doxorubicin
5. Docetaxel/gemcitabine
6. Pazopanib
7. Trabectedin
8. Eribulin
9. Other



What would be your most likely sequence of therapies for a 35-year-old patient who underwent resection of a localized undifferentiated pleomorphic sarcoma followed by radiation therapy but no adjuvant chemotherapy and now presents with larger-volume, symptomatic metastatic disease with no visceral involvement?

	First line	Second line	Third line
 MARK AGULNIK, MD	Doxorubicin	Gem/docetaxel	Pazopanib
 KRISTEN GANJOO, MD	Dox/ifos	Gem/docetaxel	Pazopanib
 SUZANNE GEORGE, MD	Dox/ifos	Gem/docetaxel	Pazopanib
 SHREYASKUMAR PATEL, MD	Dox/ifos	Gem/docetaxel	Pazopanib
 SETH M POLLACK, MD	Dox/ifos	Gem/docetaxel	Pazopanib
 RICHARD F RIEDEL, MD	Dox/ifos	Gem/docetaxel	Dacarbazine
 BRIAN A VAN TINE, MD, PHD	Dox/ifos	Gem/docetaxel	Trabectedin
 VICTOR M VILLALOBOS, MD, PHD	Dox/ifos	Gem/docetaxel	Pazopanib

Gem = gemcitabine; dox/ifos = doxorubicin/ifosfamide

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What would be your most likely sequence of therapies for a 75-year-old patient who underwent resection of a localized undifferentiated pleomorphic sarcoma followed by radiation therapy but no adjuvant chemotherapy and now presents with low-volume, asymptomatic metastatic disease?

	First line	Second line	Third line
 MARK AGULNIK, MD	Doxorubicin	Pazopanib	Gem/docetaxel
 KRISTEN GANJOO, MD	Doxorubicin	Gem/docetaxel	Pazopanib
 SUZANNE GEORGE, MD	Doxorubicin	Gem/docetaxel	Pazopanib
 SHREYASKUMAR PATEL, MD	Doxorubicin	Gem/docetaxel	Pazopanib
 SETH M POLLACK, MD	Doxorubicin	Gem/docetaxel	Pazopanib
 RICHARD F RIEDEL, MD	Liposomal doxorubicin	Gem/vinorelbine	Dacarbazine
 BRIAN A VAN TINE, MD, PHD	Doxorubicin	Gem/docetaxel	Pazopanib
 VICTOR M VILLALOBOS, MD, PHD	Doxorubicin	Gem/docetaxel	Pazopanib

Research To Practice®

What would be your most likely sequence of therapies for a 75-year-old patient who underwent resection of a localized undifferentiated pleomorphic sarcoma followed by radiation therapy but no adjuvant chemotherapy and now presents with larger volume, symptomatic metastatic disease with no visceral involvement?

	First line	Second line	Third line
 MARK AGULNIK, MD	Doxorubicin	Pazopanib	Gem/docetaxel
 KRISTEN GANJOO, MD	Gem/docetaxel	Doxorubicin	Pazopanib
 SUZANNE GEORGE, MD	Gem/docetaxel	Doxorubicin	Pazopanib
 SHREYASKUMAR PATEL, MD	Dox + dacarbazine	Gem/docetaxel	Pazopanib
 SETH M POLLACK, MD	Dox/ifos	Gem/docetaxel	Pazopanib
 RICHARD F RIEDEL, MD	Doxorubicin	Gem/vinorelbine	Dacarbazine
 BRIAN A VAN TINE, MD, PHD	Hospice or doxorubicin alone	Gem/docetaxel	Pazopanib
 VICTOR M VILLALOBOS, MD, PHD	Doxorubicin	Gem/docetaxel	Pazopanib

Gem = gemcitabine; dox = doxorubicin; ifos = ifosfamide

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What would be your most likely sequence of therapies for a 35-year-old patient who underwent resection of a localized leiomyosarcoma followed by radiation therapy but no adjuvant chemotherapy and now presents with low-volume, asymptomatic metastatic disease?

	First line	Second line	Third line
 MARK AGULNIK, MD	Doxorubicin	Trabectedin	Pazopanib
 KRISTEN GANJOO, MD	Doxorubicin	Gem/docetaxel	Pazopanib
 SUZANNE GEORGE, MD	Doxorubicin	Gem/docetaxel	Trabectedin
 SHREYASKUMAR PATEL, MD	Dox/ifos (uterine) Dox/dacarbazine (non-gyn)	Gem/docetaxel	Trabectedin
 SETH M POLLACK, MD	Doxorubicin	Trabectedin	Pazopanib
 RICHARD F RIEDEL, MD	Doxorubicin	Gem/docetaxel	Trabectedin
 BRIAN A VAN TINE, MD, PHD	Doxorubicin	Gem/docetaxel	Trabectedin
 VICTOR M VILLALOBOS, MD, PHD	Surgery (if low grade)	Pazopanib	Gem/docetaxel

Gem = gemcitabine; dox = doxorubicin; ifos = ifosfamide

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What would be your most likely sequence of therapies for a 35-year-old patient who underwent resection of a localized leiomyosarcoma followed by radiation therapy but no adjuvant chemotherapy and now presents with larger volume, symptomatic metastatic disease with no visceral involvement?

	First line	Second line	Third line
 MARK AGULNIK, MD	Doxorubicin	Gem/docetaxel	Trabectedin
 KRISTEN GANJOO, MD	Dox/ifos	Gem/docetaxel	Pazopanib
 SUZANNE GEORGE, MD	Gem/docetaxel	Doxorubicin	Trabectedin
 SHREYASKUMAR PATEL, MD	Dox/ifos (uterine) Dox/dacarbazine (non-gyn)	Gem/docetaxel	Trabectedin
 SETH M POLLACK, MD	Dox/ifos	Trabectedin	Pazopanib
 RICHARD F RIEDEL, MD	Doxorubicin/ dacarbazine	Gem/docetaxel	Trabectedin
 BRIAN A VAN TINE, MD, PHD	Dox/ifos	Gem/docetaxel	Trabectedin
 VICTOR M VILLALOBOS, MD, PHD	Surgery (if low grade)	Pazopanib	Gem/docetaxel

Gem = gemcitabine; dox = doxorubicin; ifos = ifosfamide

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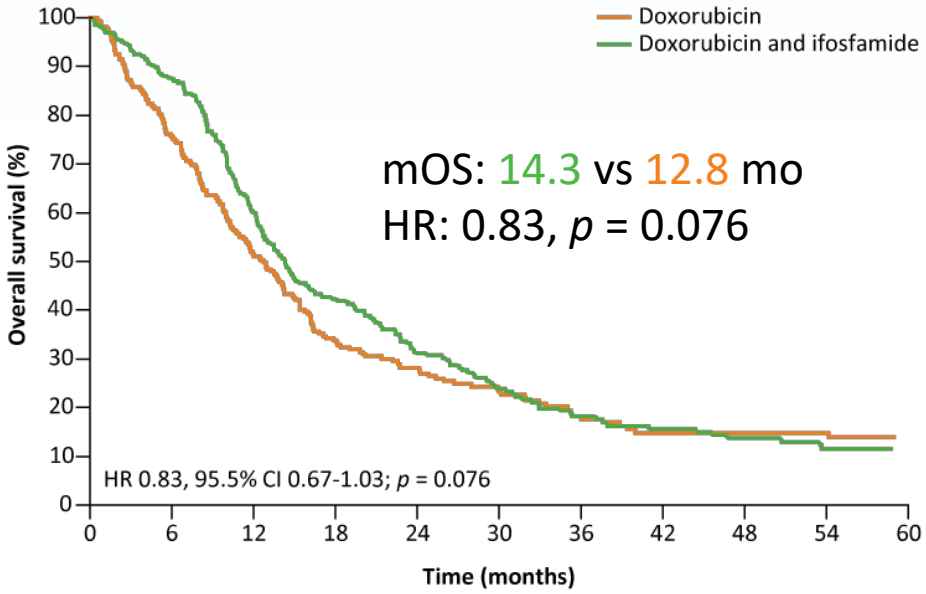
Cytotoxic Sensitivity According to STS Subtype

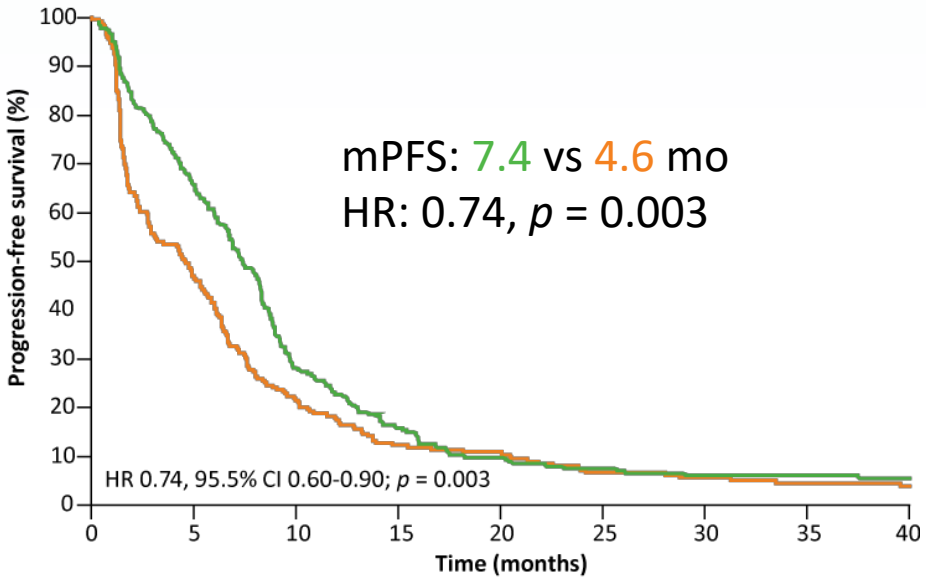
Anthracycline sensitive
• Synovial sarcoma
• Leiomyosarcoma
• Liposarcomas
• Pleomorphic sarcoma
• Angiosarcoma
• Undifferentiated pleomorphic sarcoma
• Malignant peripheral nerve sheath tumor
Resistant to anthracycline-based chemotherapy
• Alveolar soft-part sarcoma
• Clear-cell sarcoma
• Well differentiated liposarcoma
• Malignant solitary fibrous tumors

Noujaim J et al. *Int J Surg Pathol* 2016;24(1):5-15.
D'Adamo DR. *Semin Oncol* 2011;38(Suppl 3):19-29.

EORTC 62012: Doxorubicin Alone versus Intensified Doxorubicin and Ifosfamide as First-Line Therapy for Locally Advanced or Metastatic STS



mOS: 14.3 vs 12.8 mo
HR: 0.83, $p = 0.076$



mPFS: 7.4 vs 4.6 mo
HR: 0.74, $p = 0.003$

	Doxorubicin (n = 228)	Doxorubicin and ifosfamide (n = 227)
Overall response	13.6%	26.4%
Complete response	<1%	1.8%
Partial response	13%	24.7%
Stable disease	46%	50%

Judson I et al. *Lancet Oncol* 2014;15(4):415-23.

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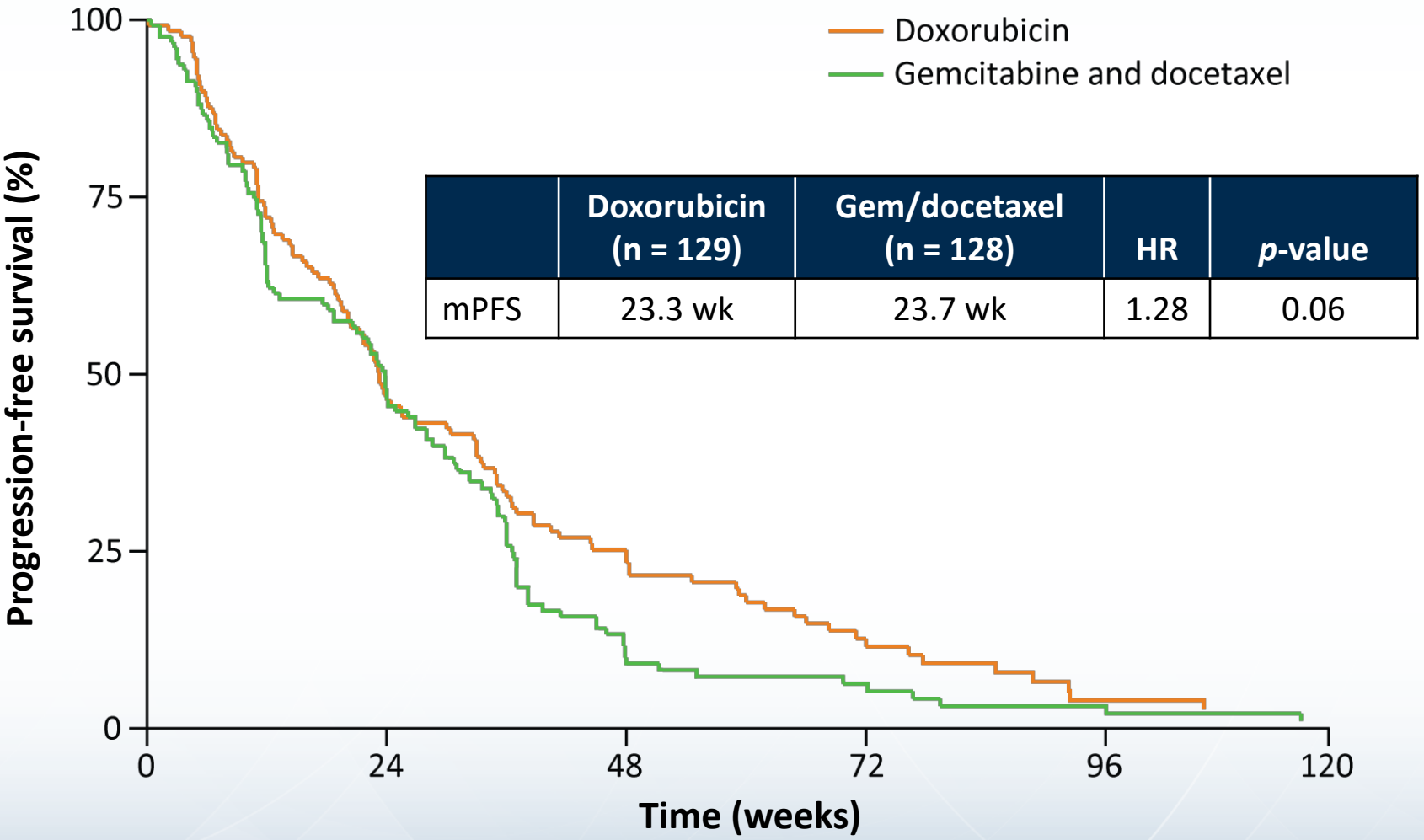
GeDDiS Phase III Study of Gemcitabine and Docetaxel vs Doxorubicin as First-Line Therapy



	Doxorubicin (n = 129)	Gem/docetaxel (n = 128)	HR	*p*-value
mPFS	23.3 wk	23.7 wk	1.28	0.06

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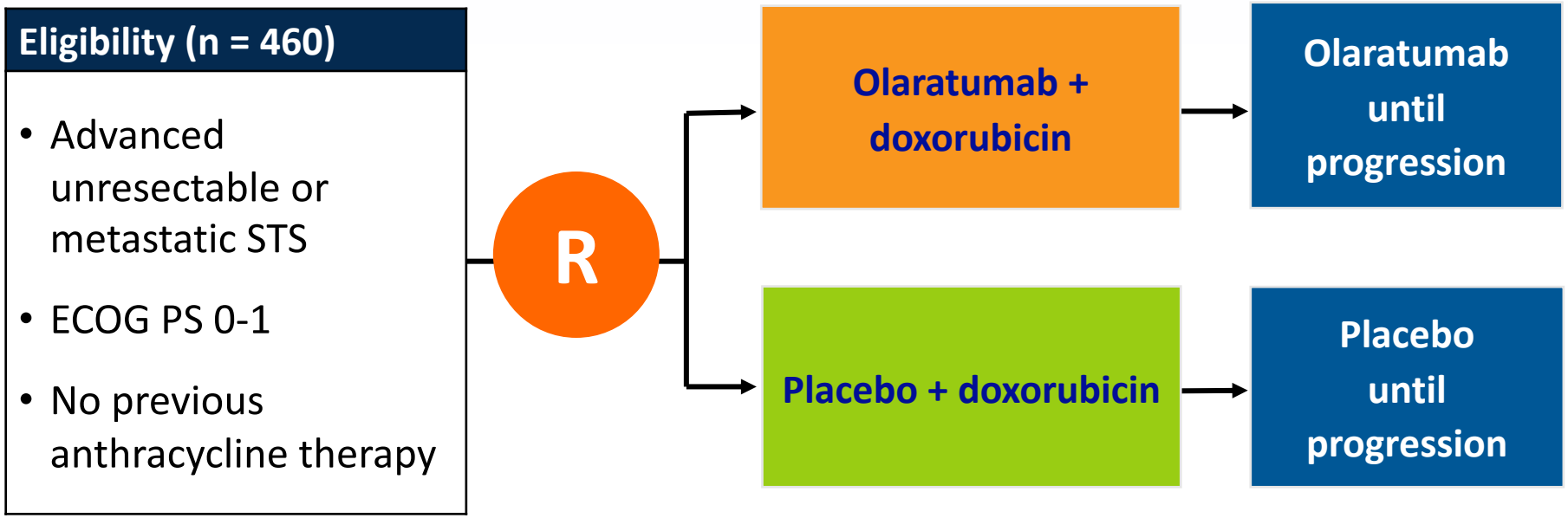
Seddon B et al. *Lancet Oncol* 2017;18(10):1397-410.

Phase III ANNOUNCE Trial Schema

Active, Not Recruiting



- **Primary endpoint:** Overall survival

Press Release: January 18, 2019: ANNOUNCE fails to meet primary endpoint

www.clinicaltrials.gov. NCT02451943 (Accessed March 2019).
https://www.prnewswire.com/news-releases/lilly-reports-results-of-phase-3-soft-tissue-sarcoma-study-of-lartruvo-300780704.html

FDA, EMA Recommend Against Starting Olaratumab for Soft Tissue Sarcoma

Press Releases: January 24 (FDA) and January 23 (EMA), 2019

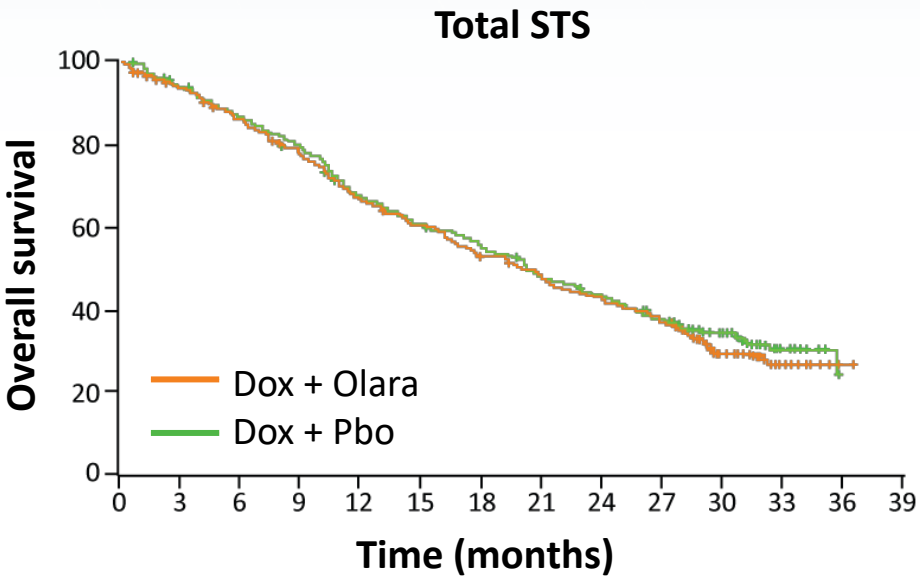
"This recently completed study did not confirm the clinical benefit of [olaratumab]. Specifically, the study did not meet the primary endpoint of improvement in overall survival for [olaratumab] and doxorubicin as compared to placebo and doxorubicin.

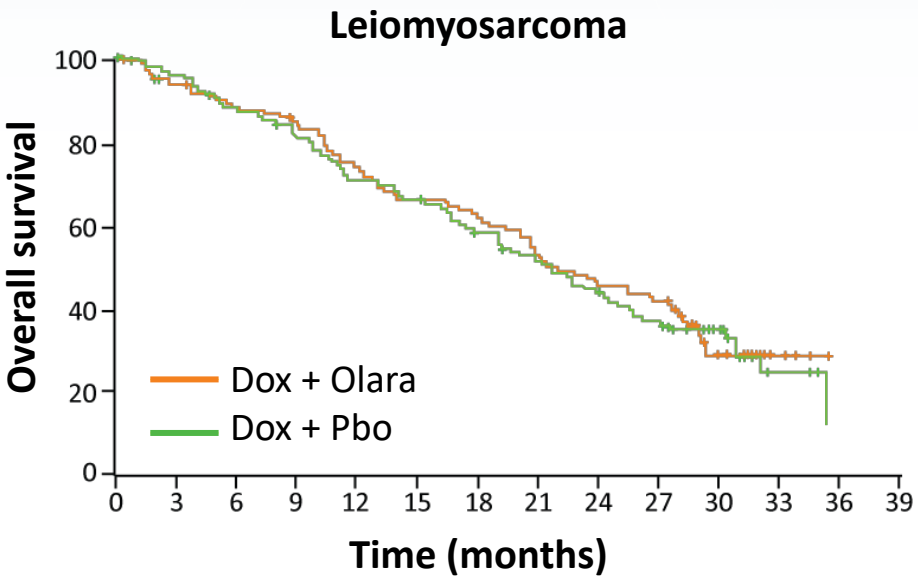
In light of this information, the FDA recommends that patients who are currently receiving [olaratumab] should consult with their healthcare provider about whether to remain on the treatment. The FDA also recommends that [olaratumab] should not be initiated in new patients outside of an investigational study.

The FDA is currently reviewing the data and working with the company to determine appropriate next steps."

https://www.ema.europa.eu/en/news/no-new-patients-should-start-treatment-lartruvo-after-study-shows-cancer-medicine-does-not-prolong
https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm526087.htm

ANNOUNCE Trial: Overall Survival in Total STS and Leiomyosarcoma Populations





OS in total STS population		
	Dox + Olara	Dox + Pbo
Median, months	20.4	19.7
Hazard ratio	1.05	
Log-rank *p*-value	0.6945	

OS in leiomyosarcoma population		
	Dox + Olara	Dox + Pbo
Median, months	21.6	21.9
Hazard ratio	0.95	
Log-rank *p*-value	0.7618	

Dox = doxorubicin; olara = olaratumab; Pbo = placebo

Tap WD et al. ASCO 2019;Abstract LBA3.

SARC Phase II Study 002: Gemcitabine (Gem) with or without Docetaxel (D) for Metastatic STS

Outcome	Gem (n = 49)	Gem-D (n = 73)	Probability Gem-D superior
CR + PR + SD >24 wk	27%	32%	Not reported
mPFS	3.0 mo	6.2 mo	0.98
mOS	11.5 mo	17.9 mo	0.97

- Compared a fixed-dose rate infusion of gemcitabine to a lower dose of gemcitabine with docetaxel
- Patients received a median of 1 prior line of therapy

Maki RG et al. *J Clin Oncol* 2007;25(19):2755-63.

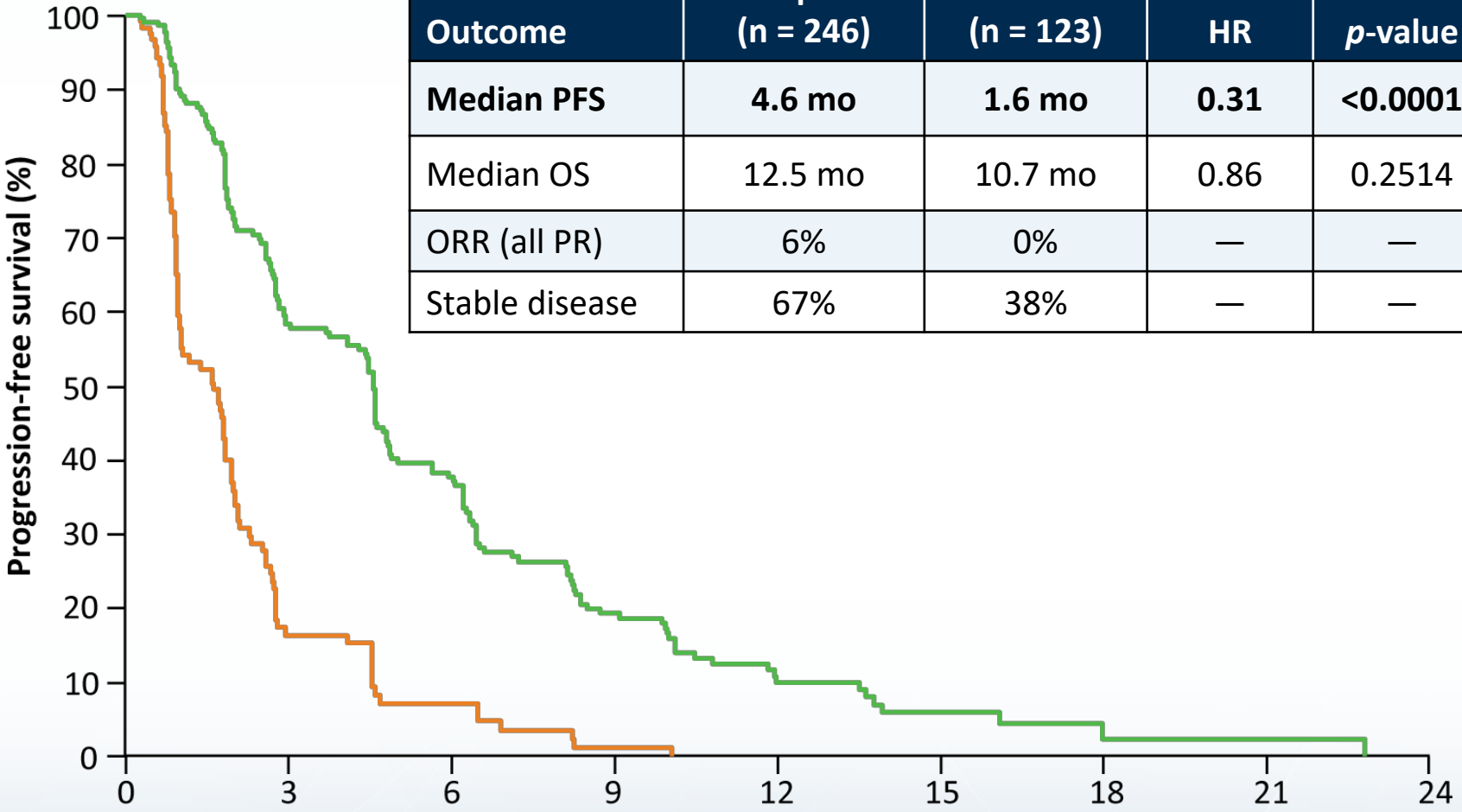
Pazopanib (FDA Approval: April 26, 2012)

- Indicated as treatment for patients with advanced STS who have received prior chemotherapy
- The efficacy of pazopanib for the treatment of adipocytic STS or GIST has not been demonstrated
- FDA approval was based on the Phase III PALETTE study (N = 369) comparing pazopanib to placebo for previously treated advanced STS

Pazopanib package insert, revised October 2016

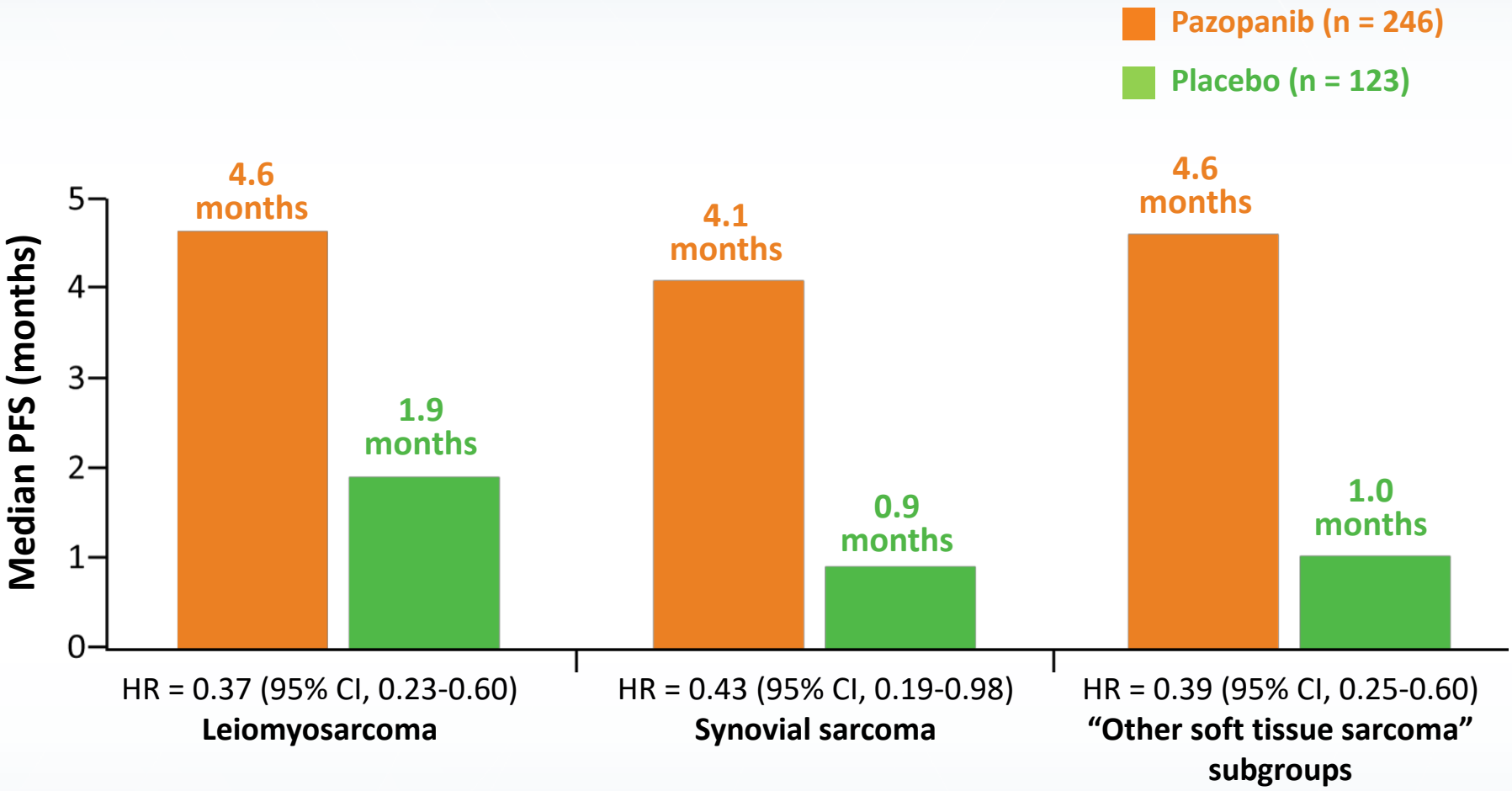
PALETTE: Survival and Response Analysis

Outcome	Pazopanib (n = 246)	Placebo (n = 123)	HR	*p*-value
Median PFS	**4.6 mo**	**1.6 mo**	**0.31**	**<0.0001**
Median OS	12.5 mo	10.7 mo	0.86	0.2514
ORR (all PR)	6%	0%	—	—
Stable disease	67%	38%	—	—



Van der Graaf WTA et al. *Lancet* 2012;379(9829):1879-86.

PALETTE: Median PFS in STS Subtypes



https://www.hcp.novartis.com/products/votrient/advanced-soft-tissue-sarcoma/efficacy/

Phase II EPAZ Study: Pazopanib versus Doxorubicin as First-Line Treatment for Metastatic STS in Elderly Patients

	Doxorubicin	Pazopanib
Survival		
Median PFS (n = 32, 74)	5.3 mo	4.4 mo
	HR = 1.00	
Median OS (n = 39, 81)	14.3 mo	12.3 mo
	HR = 1.08	
Response	**n = 39**	**n = 81**
Complete response	0	1 (1.2%)
Partial response	6 (15.4%)	9 (11.1%)
Stable disease	15 (38.5%)	41 (50.6%)
Safety	**n = 39**	**n = 81**
Neutropenia (Grade 4)	22 (56.4%)	0
Febrile neutropenia	4 (10.3%)	0

Grunwald V et al. *Proc ASCO* 2018;Abstract 11506.

Eribulin (FDA Approval: January 28, 2016)

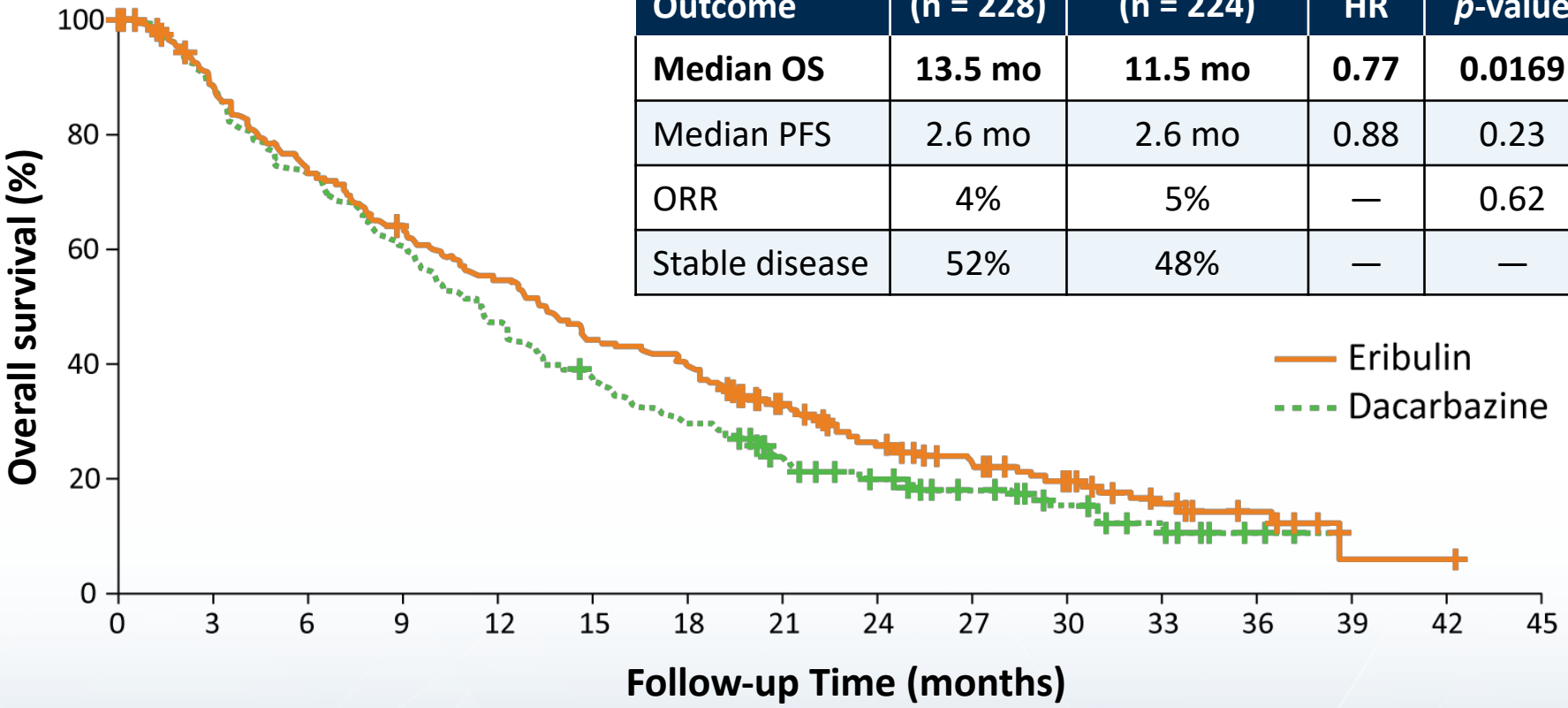
- Indicated as treatment for patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen
- FDA approval was based on a subgroup of 143 patients with advanced liposarcoma participating in the Phase III E7389-G000-309 study comparing eribulin to dacarbazine

Eribulin package insert, revised October 2016;
https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm483714.htm

Phase III E7389-G000-309 Study of Eribulin versus Dacarbazine in Previously Treated Advanced Liposarcoma and Leiomyosarcoma: Survival and Response Analysis

~100% received at least 2 lines of prior systemic therapy

Outcome	Eribulin (n = 228)	Dacarbazine (n = 224)	HR	*p*-value
Median OS	**13.5 mo**	**11.5 mo**	**0.77**	**0.0169**
Median PFS	2.6 mo	2.6 mo	0.88	0.23
ORR	4%	5%	—	0.62
Stable disease	52%	48%	—	—



Schoffski P et al. *Lancet* 2016;387(10028):1629-37.

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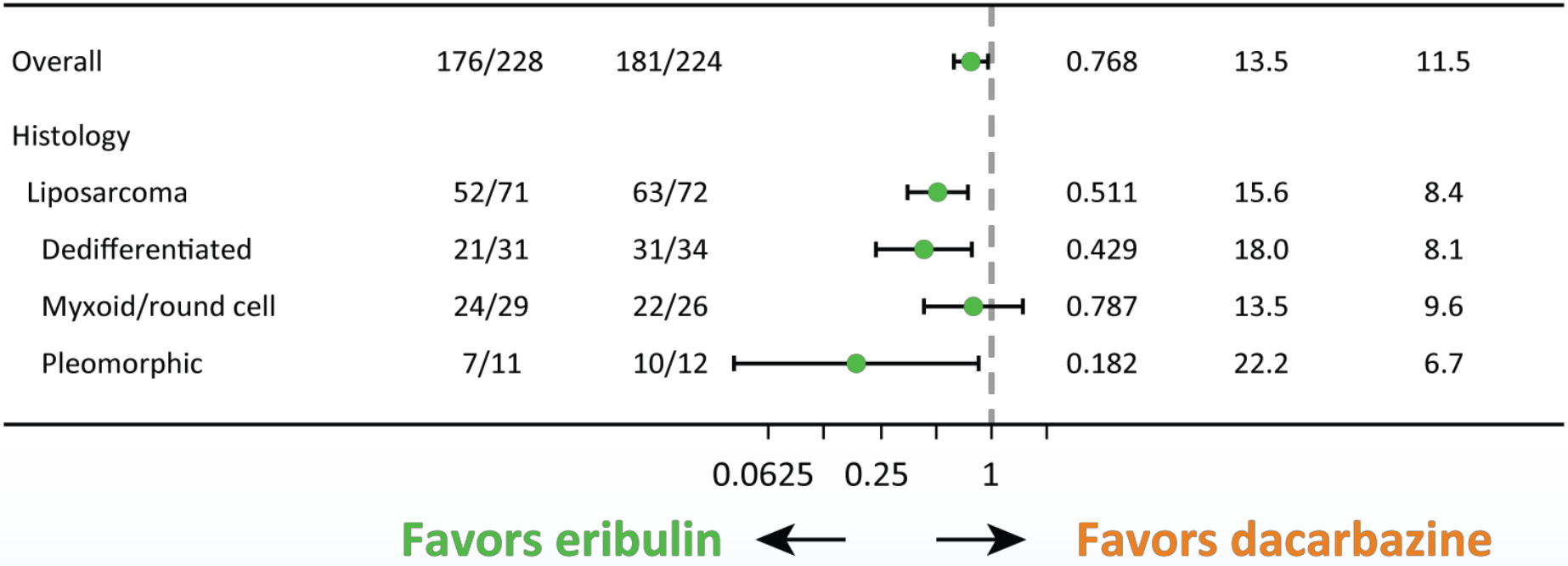
E7389-G000-309: Subgroup Analysis of Overall Survival for Patients with Advanced Liposarcoma

Group/Subgroup	Events/No. Eribulin	Events/No. Dacarbazine	HR	Median (months) Eribulin	Median (months) Dacarbazine
Overall	176/228	181/224	0.768	13.5	11.5
Histology					
Liposarcoma	52/71	63/72	0.511	15.6	8.4
Dedifferentiated	21/31	31/34	0.429	18.0	8.1
Myxoid/round cell	24/29	22/26	0.787	13.5	9.6
Pleomorphic	7/11	10/12	0.182	22.2	6.7



Demetri GD et al. *J Clin Oncol* 2017;35(30):3433-9.

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Trabectedin (FDA Approval: Oct 23, 2015)

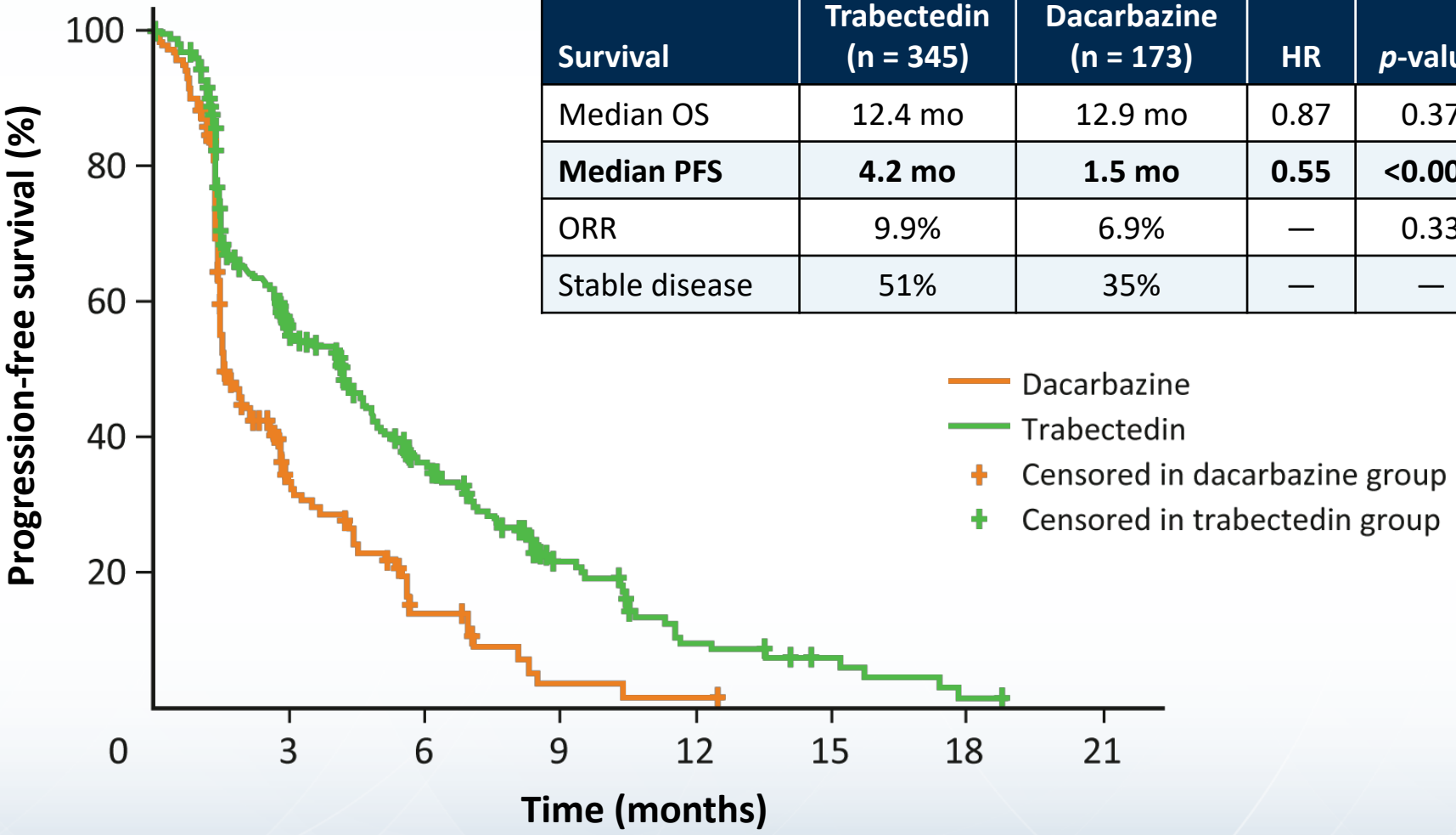
- Indicated as treatment for patients with unresectable or metastatic ***liposarcoma or leiomyosarcoma*** who received a prior anthracycline-containing regimen
- FDA approval was based on the Phase III ET743-SAR-3007 study (N = 518) comparing trabectedin to dacarbazine

www.cancer.gov/news-events/cancer-currents-blog/2015/fda-trabectedin-sarcoma
Trabectedin package insert, revised June 2018

ET743-SAR-3007: Survival and Response Analyses

88% received at least 2 lines of prior systemic therapy

Survival	Trabectedin (n = 345)	Dacarbazine (n = 173)	HR	*p*-value
Median OS	12.4 mo	12.9 mo	0.87	0.37
Median PFS	**4.2 mo**	**1.5 mo**	**0.55**	**<0.001**
ORR	9.9%	6.9%	—	0.33
Stable disease	51%	35%	—	—



Demetri GD et al. *J Clin Oncol* 2016;34(8):786-93.

Phase III T-SAR Trial: Trabectedin versus Best Supportive Care (BSC) for Patients with Pretreated Advanced STS

	Trabectedin	BSC	HR	*p*-value
ITT Population	**n = 52**	**n = 51**		
Median PFS	3.12 mo	1.51 mo	0.39	<0.0001
ORR (all PR) SD	13.7% 66.7%	0% 61.2%	—	—
L-Sarcomas	**n = 32**	**n = 30**		
Median PFS	5.13 mo	1.41 mo	0.29	<0.0001
ORR (all PR) SD	21.9% 65.6%	0% 64.3%	—	—
Non L-Sarcomas	**n = 20**	**n = 21**		
Median PFS	1.81 mo	1.51 mo	0.60	0.16
ORR SD	0% 68.4%	0% 57.1%	—	—

Approximately 88% received at least 1 prior line of systemic therapy for advanced disease

Le Cesne A et al. *Proc ASCO* 2018;Abstract 11508.

Management of Soft Tissue Sarcoma (STS)

MODULE 1: Overview of STS; Initial Workup and Classification

- Incidence, biology and histopathologic classification
- Biopsy technique; imaging workup
- Indications for involvement of specialized tertiary care providers

MODULE 2: Management of Localized Disease

- Role of neoadjuvant/adjuvant radiation therapy
- Role of neoadjuvant/adjuvant chemotherapy

MODULE 3: Management of Metastatic STS

- Local treatment of oligometastatic disease
- Selection and sequencing of systemic treatments
- Investigational strategies and agents

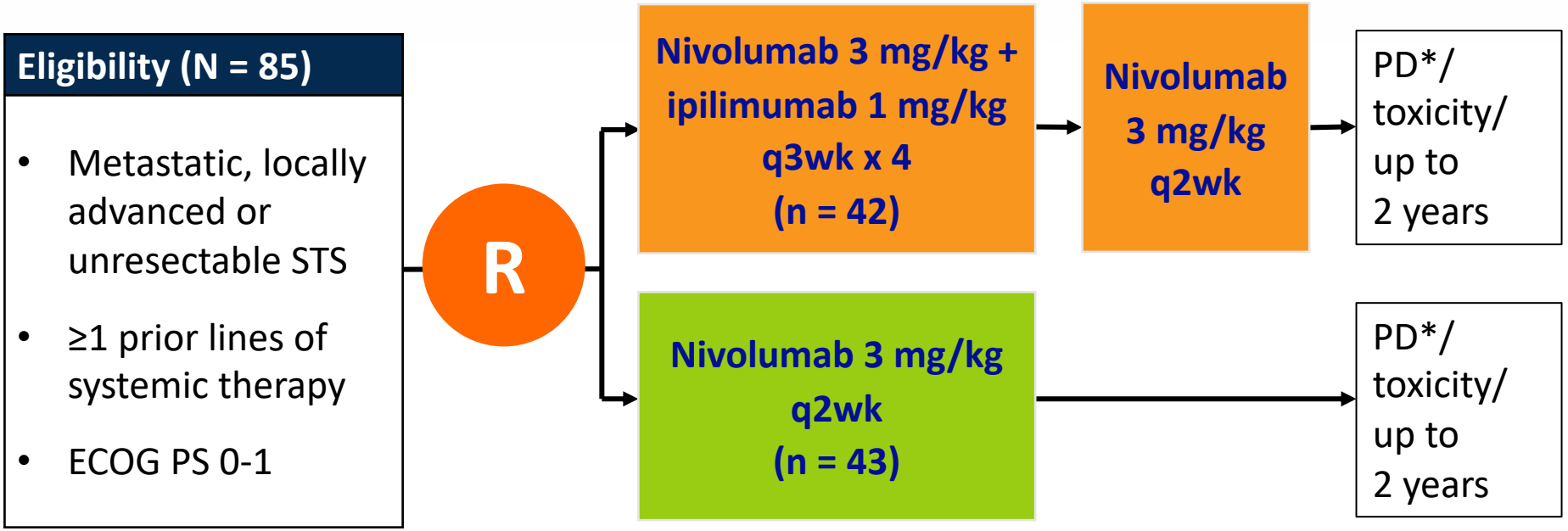
SARC028: A Phase II Study of Pembrolizumab in Advanced STS and Bone Sarcoma

Sarcoma subtype (N = 40 in STS cohort)	CR	PR	SD
Undifferentiated pleomorphic sarcoma (n = 10)	1 (10%)	3 (30%)	3 (30%)
Liposarcoma (n = 10)	0	2 (20%)	4 (40%)
Synovial sarcoma (n = 10)	0	1 (10%)	2 (20%)
Leiomyosarcoma (n = 10)	0	0	6 (60%)

- Two (5%) of 40 patients with bone sarcoma had an objective response:
  - One (5%) of 22 patients with osteosarcoma
  - One (20%) of 5 patients with chondrosarcoma

Tawbi HA et al. *Lancet Oncol* 2017;18(11):1493-501.

Alliance A091401: Two Open-Label, Noncomparative, Randomized Phase II Trials



* Treatment beyond PD permitted in first 12 weeks

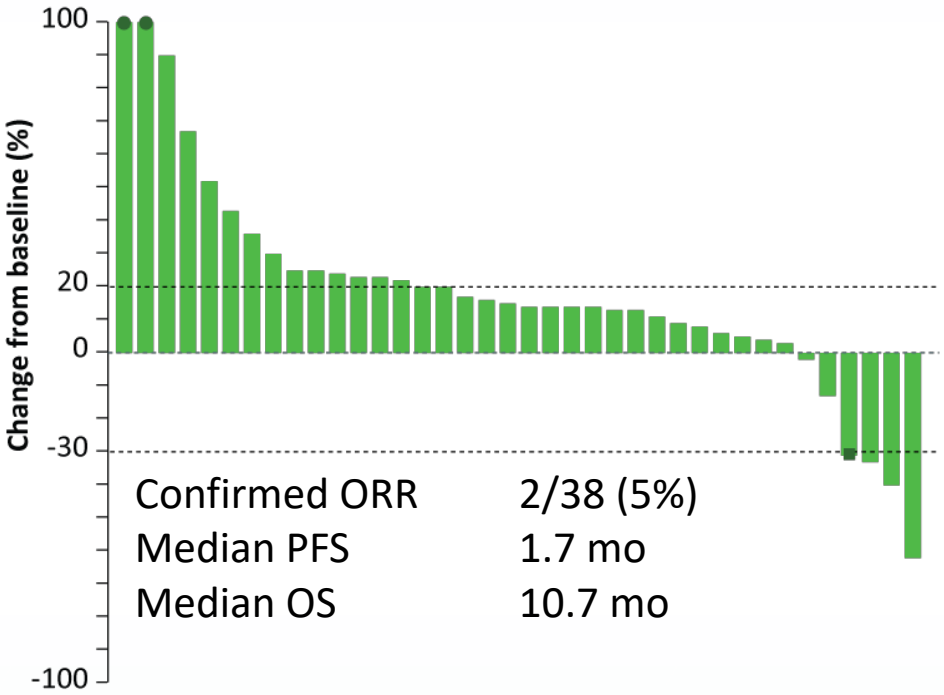
Primary endpoint: Confirmed objective response rate
Secondary endpoints: DoR, CBR, PFS and OS

D'Angelo SP et al. *Lancet Oncol* 2018;19(3):416-26.

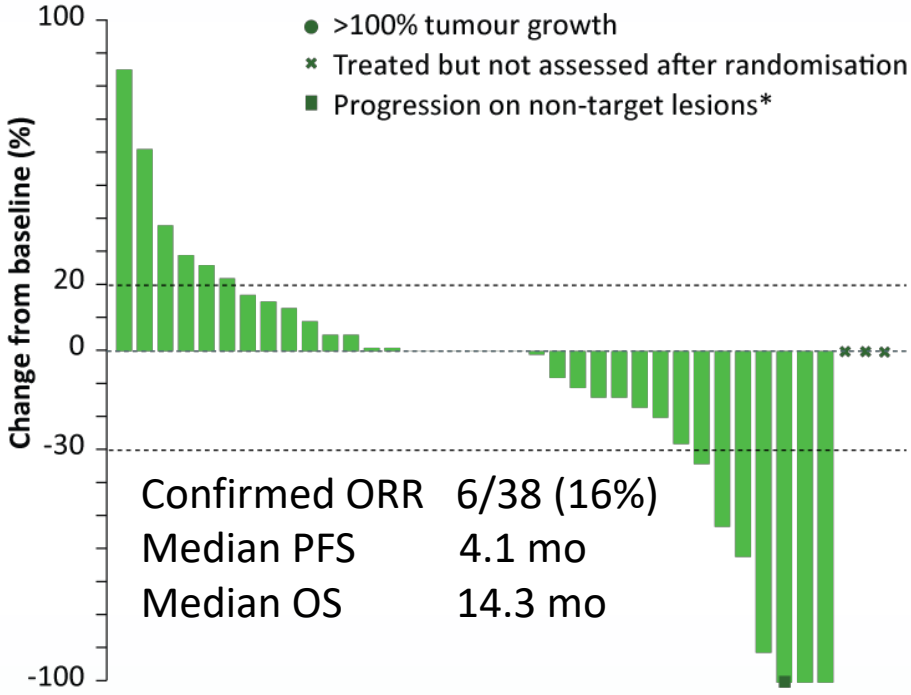
Research To Practice®

Alliance A091401: Nivolumab with or without Ipilimumab for Advanced Sarcoma

Nivolumab Monotherapy



Nivolumab/Ipilimumab



* Patient achieved PR according to radiographic assessments but was classified as PD by unequivocal PD on nontarget lesions.

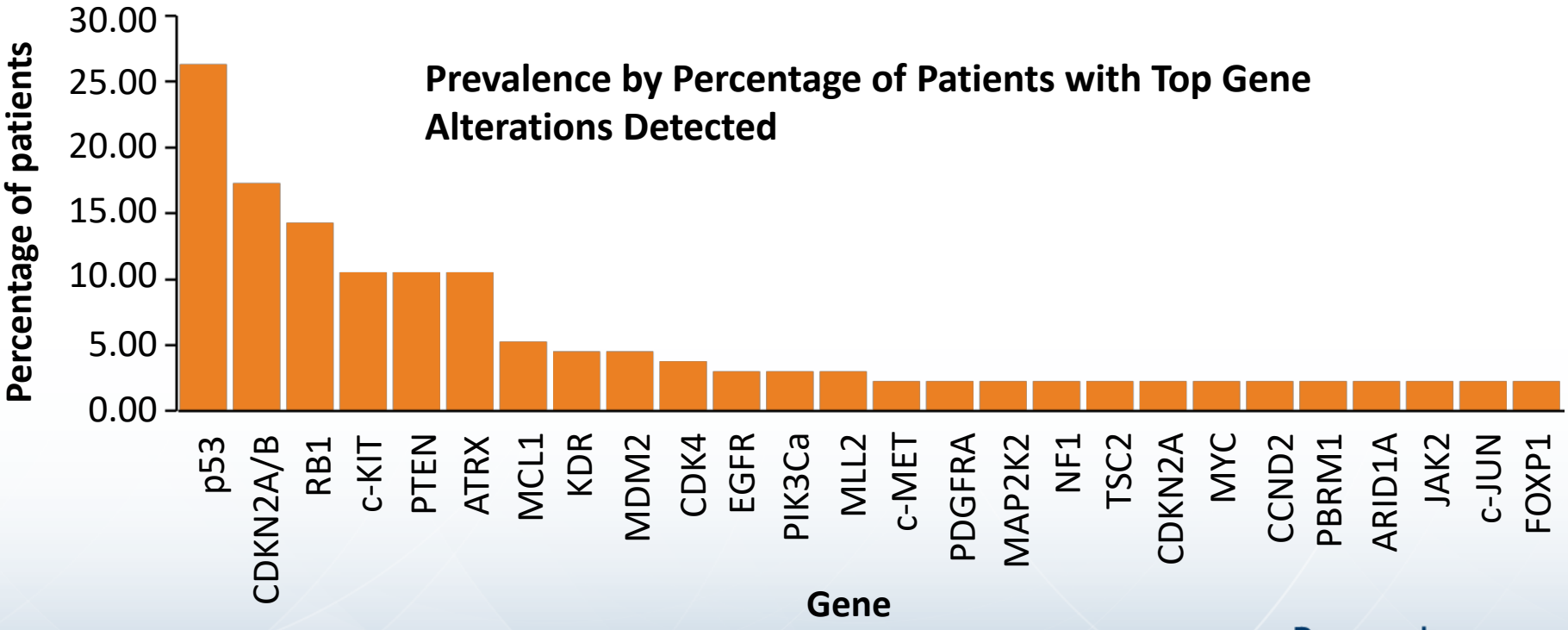
Cases were heavily pretreated, with 52 (61%) of 85 patients having received at least 3 previous lines of therapy.

D'Angelo SP et al. *Lancet Oncol* 2018;19(3):416-26.

Research To Practice®

Next-Generation Sequencing for Patients with Sarcoma

- Retrospective NGS analysis of 133 tumor samples from patients diagnosed with a variety of sarcomas at Massachusetts General Hospital
- 2 gene alterations identified per tumor sample (range: 0-14)
- 88% had at least 1 mutation detected
- 75 mutations detected in genes that were targetable with existing drugs



Cote GM et al. *Oncologist* 2018;23(2):234-42.

Questions?

To view the slides please visit
www.ResearchToPractice.com/Meetings/Slides

Visiting Professors: Investigator Perspectives on the Management of Soft Tissue Sarcoma

An Interactive Grand Rounds Series

Mark Agulnik, MD
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Chicago, Illinois

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To Practice®