
Sarcoma Management in North Carolina: Updates for 2023
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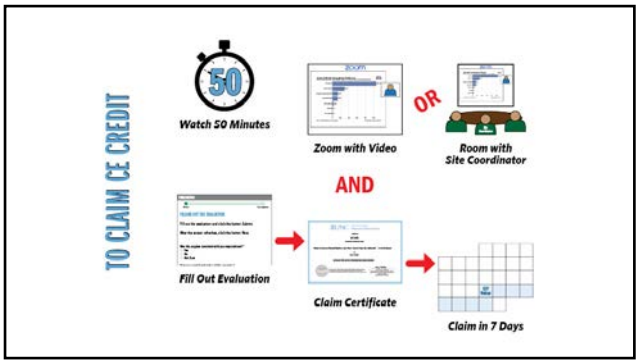
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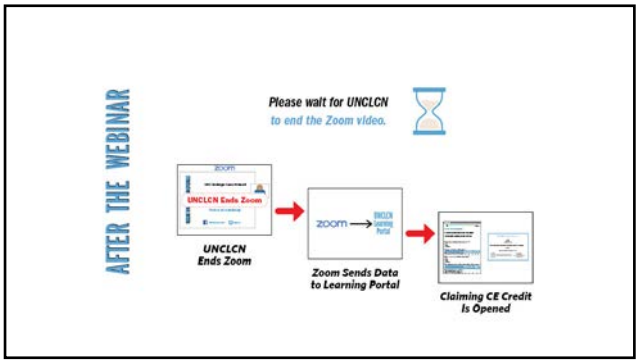
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RESEARCH TO PRACTICE
Mark Woodcock, MD
Sarcoma Management in North Carolina: Updates for 2023
July 26

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OUR PRESENTER

Mark Woodcock, MD

Mark Woodcock, MD, received his medical degree from University of Louisville School of Medicine.

In 2019, the Lung Cancer Initiative of North Carolina awarded him with a Fellowship Grant to support a research effort to identify characteristics of lung cancer patients who respond to treatments that unlock the immune system against cancer.

He was named as the 2019 Lung Cancer Initiative Outstanding Fellow Applicant.

He works to apply analytical and machine learning techniques to large datasets for answering genomic questions in oncology and immunology.

Dr. Woodcock is a hematology and oncology specialist with the Division of Oncology in the UNC School of Medicine.

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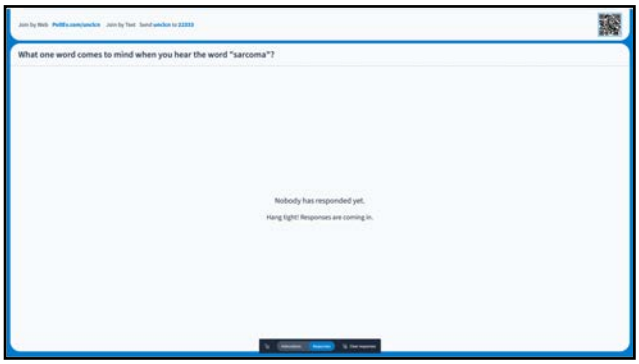

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The presenter has no relevant financial relationships with ineligible companies as defined by the ACCME.

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What one word comes to mind when you hear the word "sarcoma"?

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UNC CANCER CARE

Sarcoma Management in North Carolina: Updates for 2023

Mark Woodcock, MD
Bone and Soft Tissue Oncology Program
Department of Medicine, Division of Oncology

Lineberger Comprehensive Cancer Center
UNC School of Medicine
The University of North Carolina at Chapel Hill

July 26, 2023

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Conflicts of Interest & Disclosures

Mark Woodcock, MD: None

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Question #1

A 68 yo male with history of obesity and HTN is referred to your clinic after noticing a lump on his back. He's not sure how long it has been there or if has changed.

On exam you note a soft, 2x2cm mass just superior and medial to the left scapula and below the dermis without overlying skin changes. It is non-tender to palpation and easily mobilized.

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Overview

1. **Epidemiology**
2. **Suspicion and initial workup**
3. **(Neo)Adjuvant approaches**
4. **Metastatic disease**

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Topics for another day

- Gastrointestinal stromal tumors
- Young adult / pediatric tumors
  - Ewing sarcoma
  - Rhabdomyosarcoma
- Bone and chondroid sarcomas
- Ultra-rare subtypes

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Terminology

- STS: Soft Tissue Sarcoma
  - liposarcoma
  - leiomyosarcoma
  - undifferentiated pleomorphic sarcoma
  - ?GIST
- Bone Sarcoma
  - Ewing sarcoma
  - Osteosarcoma

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Epidemiology

- 13,400 new cases[1] expected in the United States in 2023

24 1. American Cancer Society: https://www.cancer.org/cancer/types/soft-tissue-sarcoma/about/key-statistics.html UNC LINEBERGER COMPREHENSIVE CANCER CENTER

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Epidemiology

- **13,400 new cases[1] expected in the United States in 2023**
  - **1:25,000 (sarcoma) 1:624 (breast in women) 1:575 (prostate in men)**

25 1. American Cancer Society: https://www.cancer.org/cancer/types/soft-tissue-sarcoma/about/key-statistics.html

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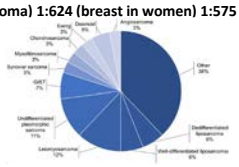

26 1. American Cancer Society: https://www.cancer.org/cancer/types/soft-tissue-sarcoma/about/key-statistics.html
2. Gamboa AC, Gronchi A, Cardona K. Soft-tissue sarcoma in adulthood and childhood: an ongoing tale of heterogeneity and specific management in an era of personalized medicine. CA Cancer J Clin. 2020 May;70(3):200-229. PMID: 32275330.

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Epidemiology

- **2021 French sarcoma reference center review[1] (n=18712):**
  - **Central review**
  - **150+ subtypes**

Histologic grouping	Incidence per million persons per year
Undifferentiated pleomorphic sarcoma	5.9
Leiomyosarcoma	9.7
Malignant lipomatous tumors	12.3
GIST	12.4 ***
Osteosarcoma, high grade varieties	5.5
Ewing sarcoma	2.3

27 1. de Pinieux G, et al.. Nationwide incidence of sarcoma and connective tissue tumors of intermediate malignancy over four years using an expert pathology review network. PLoS One. 2021 Feb 25;16(2):e0246958. PMID: 33630918; PMCID: PMC7906477.

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Suspicion, workup and diagnosis

Lumps are common, sarcomas are rare

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Question #2

A 68 yo male with history of obesity and HTN is referred to your clinic after noticing a lump on his back. He's not sure how long it has been there or if has changed.

On exam you note a 6x4cm "bulge" just superior and medial to the left scapula without overlying skin changes. The area is non-tender, firm, and immobile.

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Signs, Symptoms, and Suspicion

- **Soft tissue masses**
  - Lump > 5cm
  - Increasing in size over time
  - Deep to fascia
  - Pain

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1. "Improving Outcomes for People with Sarcoma", NHS/National Institute for Health and Clinical Excellence, March 2006

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Signs, Symptoms, and Suspicion

- **Bone lesions**
  - Age < 40 + Symptomatic + abnormal radiograph
    - Immediate and urgent referral
  - Age >= 40
    - Workup for metastatic disease if clinically indicated, otherwise urgent referral

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1. "Bone Cancer", NCCN Clinical Practice Guidelines in Oncology, Version 3.2023 (Apr 4, 2023)

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Signs, Symptoms, and Suspicion

- **Inherited syndromes**
  - Carney-Stratakis (germline SDH)
  - Li-Fraumeni syndrome
  - HNPCC / Lynch syndrome
  - FAP
  - Neurofibromatosis

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Urgency in Bone Sarcoma

- **What's the hurry?**
  - Early identification of Ewing-spectrum and osteosarcomas
  - Potentially curable
  - Rapid growth
  - Require multidisciplinary treatment plans
  - Ideally neoadjuvant chemotherapy

- n.b. there are some STSs where this also applies:
  - Round cell sarcomas
  - Rhabdomyosarcoma

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Tissue diagnosis

- **Extremity, body wall, or head and neck sarcomas**
  - Core needle [NCCN preferred] or incisional biopsy
    - Pathologic workup often requires multiple sections for staining
    - Molecular testing frequently desirable
  - Biopsy path along future resection axis
- **Abdominal / Retroperitoneal**
  - Consider biopsy when:
    - Possible neoadjuvant chemotherapy
    - Non-sarcoma histology suspected

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Tissue diagnosis

- **Expert pathologists change dx frequently[1,2]**
  - NCCN: "Pathologic assessment of biopsies and resection specimens should be carried out by an experienced sarcoma pathologist"

1. Ray-Coquard I, et al. Sarcoma: concordance between initial diagnosis and centralized expert review in a population-based study within three European regions. Ann Oncol. 2012 Sep
2. Theay K, et al. Histopathological diagnostic discrepancies in soft tissue tumours referred to a specialist centre: reassessment in the era of ancillary molecular diagnosis. Sarcoma. 2014

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Staging Imaging in STS

- **Extremity tumors: MRI for surgical planning**
- **Deep tissue / trunk lesions: Contrasted CT**
- **Metastatic disease evaluation: Non-contrast chest CT**

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Staging Imaging in STS

- **Special considerations**
  - **Myxoid / Round cell liposarcoma**
    - **Total spine MR**
    - **Total body MR**
  - **CNS imaging:**
    - **Angiosarcoma**
    - **Alveolar soft part sarcoma**
    - **Left-sided intra-cardiac sarcomas**

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Staging Imaging in STS

- **Imaging of regional lymph node basin**
  - **Not routinely utilized**
  - **Exceptions**
    - **Angiosarcoma**
    - **Rhabdomyosarcoma**
    - **Synovial sarcoma**
    - **Clear cell sarcoma**
    - **Epithelioid sarcoma**

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Staging Imaging in STS

- **PET/CT**
  - **Not routinely utilized**
  - **Exceptions**
    - **Small round cell sarcoma**
    - **Angiosarcoma**
    - **MPNST**

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Molecular testing

- **Increasingly useful in diagnostic workup**
  - **Less informative for therapeutics in 2023**
  - **Commonly:**
    - **MDM2, CDK4 amplifications:** de-differentiated liposarcoma
    - **APC mutations:** Desmoid tumors (FAP related)
    - **KIT, PDGFRA:** Gastrointestinal stromal tumors
    - **Diagnostic gene fusions**

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TUMOR	ABBREVIATION	GENE(S) INVOLVED
Malignant Round Cell Tumors - continued		
Undifferentiated round cell sarcoma	t(4;19)(q35;q13) or t(10;19)(q26;q13)	CIC-DUX4[a]
	t(x;22)(p11.2;q12.2)	BCOR-CCNB3[a]
Lipomatous Tumors		
Atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLS)	Supernumerary ring chromosome; giant marker chromosomes	Amplification of region 12q14-15, including MDM2, CDK4, HMGA2, SAS, CPM
Dedifferentiated liposarcoma	Same as for ALT/WDLS	Same as for ALT/WDLS
Myxoinflammatory cell liposarcoma	t(12;16)(q13;p11)	FUS-DDIT3
	t(12;22)(q13;q12)	EWSR1-DDIT3
Pleomorphic liposarcoma	Complex alterations	Unknown
Other Sarcomas		
Alveolar soft part sarcoma	der(17)(X;17)(p11.q25)	ASPL-TFE3
Angiomatoid fibrous histiocytoma	t(12;22)(q13;q12)	EWSR1-ATF1
	t(2;22)(q33;q12)	EWSR1-CREB1
	t(12;16)(q13;p11)	FUS-ATF1
Clear cell sarcoma	t(12;22)(q13;q12)	EWSR1-ATF1
	t(2;22)(q32;q12)	EWSR1-CREB1
Congenital/infantile fibrosarcoma	t(12;15)(p13;q25)	ETV6-NTRK3[a]
Dermatofibrosarcoma protuberans	t(17;22)(q21;q13) and derivative ring chromosomes	COL1A1-PDGFB
Desmoid fibromatosis	Trisomy 8 or 20; loss of 5q21	CTNNB1 or APC mutations
High-grade endometrial stromal sarcoma	t(10;17)(q22;p13)	YWHAE-NUTM2
	t(x;22)(p11.q12)	ZC3H7B-BCOR[a]
TUMOR	**ABBREVIATION**	**GENE(S) INVOLVED**
Malignant Round Cell Tumors		
Alveolar RMS	t(2;13)(q35;q14)	PAX3-FOXO1
	t(1;13)(p36;q14)	PAX7-FOXO1
	t(X;2)(q13;q35)	PAX3-AFX
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	EWSR1-WT1
Embryonal RMS	Complex alterations	Multiple: MYOD1, ARAS, HRAS, TP53, NF1, NRAS, PIK3CA, FBXW7, FGFR4, BCOR
Ewing sarcoma/peripheral neuroectodermal tumor	t(11;22)(q24;q12)	EWSR1-FLI1
	t(21;22)(q22;q12)	EWSR1-ERG
	t(2;22)(q33;q12)	EWSR1-FEV
	t(7;22)(p22;q12)	EWSR1-ETV1
	t(17;22)(q12;q12)	EWSR1-E1AF
	inv(22)(q12q12)	EWSR1-ZSG
	t(16;22)(p11;q12)	FUS-ERG

TUMOR	ABBREVIATION	GENE(S) INVOLVED
Epithelioid hemangioendothelioma	t(1;10)(p36;q11)	WWTR1-CAMTA1
	t(3;11)(q25;p11.2)	YAP1 - TFE3
Epithelioid sarcoma	Inactivation, deletion, or mutation of INI1 (SMARCB1)	INI1 (SMARCB1)
Extraskeletal myxoid chondrosarcoma	Inactivation of INI1 (SMARCB1)	INI1 (SMARCB1)
Extraskeletal myxoid chondrosarcoma	t(9;22)(q31;q12)	EWSR1-NR4A3
	t(9;17)(q22;q11)	TAF15-NR4A3
	t(9;15)(q22;q21)	TCF12-NR4A3
	t(3;9)(q11;q22)	TFG-NR4A3
Gastrointestinal stromal tumor (GIST)	Activating kinase mutations	KIT or PDGFRA
Kidney cancer	Kidney cancer mutations	Germline SDH subunit mutations
Leiomyosarcoma	t(1;3)(p22;q21)	TPM3-ALK[a]
	t(2;5)(p23;q35)	CLTC-ALK[a]
	t(2;17)(p23;q23)	TFG-ALK[a]
	t(2;19)(p23;q13)	RANBP2-ALK[a]
	t(2;3)(p23;q21)	ATIC-ALK[a]
	t(2;3)(p23;q21)	ALK-ATIC[a]
	inv(2)(p23q35)	EML4-ALK[a]
	t(2;17)(p23;q23)	TPR-ALK[a]
Low-grade fibromyxoid sarcoma	Complex alterations	Unknown
	t(7;16)(q34;p11)	FUS-CREB3L2
	t(11;16)(p11;p11)	FUS-CREB3L1
Malignant peripheral nerve sheath tumor		NF1, CDKN2A and SUZ12 or EED
Mesenchymal chondrosarcoma	t(8;16)(q13;p11)	HEY1 - NCOA2
Solitary fibrous tumor	inv(12)(q13q13)	NAB2 - STAT6
Synovial sarcoma	t(X;18)(p11.2;q11); t(X;18)(p11.2;q11); t(X;18)(p11.2;q11)	SS18-SSX1, SS18-SSX2, SS18-SSX4
Tenosynovial giant cell tumor/pigmented villonodular synovitis (TGCT/PVNS)	t(1;12)(p13;q15)	CSF1

1. "Soft Tissue Sarcoma", NCCN Clinical Practice Guidelines in Oncology, Version 2.2022 (May 17, 2022)

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Adjuvant therapy

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Adjuvant chemotherapy

Adjuvant CYVADIC Chemotherapy for Adult Soft Tissue Sarcoma—Reduced Local Recurrence but No Improvement in Survival: A Study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group

By Vivien Bramwell, Jacques Rouesse, Will Steward, Armando Santoro, H. Schrafforde-Koops, Jose Bueso, Wlodzimierz Ruka, Julio Priario, Theo Wagener, Marion Burgers, Jan Van Unnik, Genevieve Contesso, Denis Thomas, Martine van Glabbeke, David Markham, and Herbert Pinedo

1. Bramwell V, et al. Adjuvant CYVADIC chemotherapy for adult soft tissue sarcoma--reduced local recurrence but no improvement in survival: a study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol. 1994

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Adjuvant chemotherapy

Cochrane Library — Trusted evidence. Informed decisions. Better health.

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[Intervention Review]

Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults

Sarcoma Meta-analysis Collaboration (SMAC) - see acknowledgement section for list of authors[1]

1. Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults. Sarcoma Meta-analysis Collaboration (SMAC). Cochrane Database Syst Rev. 2000

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Adjuvant chemotherapy

Cochrane

Adjuvant Chemotherapy for Adult Soft Tissue Sarcomas of the Extremities and Girdles: Results of the Italian Randomized Cooperative Trial

By Sergio Frustaci, Franco Gherlinzani, Antonino De Paoli, Marco Bonetti, Alberto Azzarelli, Alessandro Comandone, Patrizia Olmi, Angela Buonadonna, Giovanni Pignatti, Enzo Barbieri, Gaetano Apice, Hassan Zmerly, Diego Serraino, and Piero Picci

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1. Frustaci S, Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. J Clin Oncol. 2001

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Adjuvant chemotherapy

Cochrane

Ifosfamide in the Adjuvant Therapy of Soft Tissue Sarcomas

S. Frustaci[a] A. De Paoli[b] E. Bidoli[c] N. La Mura[a] M. Berretta[a]
A. Buonadonna[a] G. Boz[b] F. Gherlinzoni[d]
on behalf of the Italian Sarcoma Group and the Participating Centers

Departments of [a]Medical Oncology, [b]Radiation Oncology and [c]Epidemiology and Biostatistics, Centro di Riferimento Oncologico di Aviano and [d]Division of Orthopedics, General Hospital, Gorizia, Italy

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1. Frustaci S, Ifosfamide in the adjuvant therapy of soft tissue sarcomas. Oncology. 2003

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Adjuvant chemotherapy

Cochrane

A Systematic Meta-Analysis of Randomized Controlled Trials of Adjuvant Chemotherapy for Localized Resectable Soft-Tissue Sarcoma

Nabeel Pervaiz[1], Nigel Colterjohn, MD[2], Forough Farrokhyar, MPH, PhD[2], Richard Tozer, MD, PhD[3], Alvaro Figueredo, MD[3], Michelle Ghert, MD[3]

BACKGROUND. The use of adjuvant chemotherapy to treat adults with localized resectable soft-tissue sarcoma remains controversial. The objective of this systematic review was to update the 1997 meta-analysis of randomized controlled trials (RCTs) to reassess the efficacy of doxorubicin-based chemotherapy with respect to recurrence and survival.

METHODS. A comprehensive literature search was performed to identify RCTs of

48

1. Pervaiz N. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer. 2008

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Adjuvant chemotherapy

Intensified adjuvant IFADIC chemotherapy in combination with radiotherapy *versus* radiotherapy alone for soft tissue sarcoma: long-term follow-up of a prospective randomized feasibility trial

Negar Fakhrai[1,2], Claudia Ebm[1], Wolfgang J. Kostler[1], Marion Jantsch[1], Farshid Abdolvahab[1], Martin Dominkus[1], Boris Pokrajac[1], Daniela Kauer-Dorner[1], Christoph C. Zielinski[1,3], Thomas Brodowicz[1]; for the Austrian Cooperative Soft Tissue Sarcoma Study Group

1. Fakhrai N, Intensified adjuvant IFADIC chemotherapy in combination with radiotherapy versus radiotherapy alone for soft tissue sarcoma: long-term follow-up of a prospective randomized feasibility trial. Wien Klin Wochenschr. 2010 Nov

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Adjuvant chemotherapy

Effect of adjuvant chemotherapy on survival in FNCLCC grade 3 soft tissue sarcomas: a multivariate analysis of the French Sarcoma Group Database

A. Italiano[1*], F. Delva[2,3], S. Mathoulin-Pelissier[2,3], A. Le Cesne[4], S. Bonvalot[5], P. Terrier[6], M. Trassard[7], J.-J. Michels[8], J.-Y. Blay[9], J.-M. Coindre[10] & B. Bui[1]

1. Italiano A, Effect of adjuvant chemotherapy on survival in FNCLCC grade 3 soft tissue sarcomas: a multivariate analysis of the French Sarcoma Group Database. Ann Oncol. 2010 Dec

50

Adjuvant chemotherapy

Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial

1. Woll PJ, et al. Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial. Lancet Oncol. 2012 Oct

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Adjuvant chemotherapy

Adjuvant Chemotherapy for Adult Soft Tissue Sarcomas of

A Systematic Meta-Analysis of Randomized Controlled

Intensified adjuvant IFADIC chemotherapy in combination

Effect of adjuvant chemotherapy on survival in FNCLCC

Adjuvant chemotherapy with doxorubicin, ifosfamide, and

Doxorubicin-based adjuvant chemotherapy in soft tissue sarcoma: pooled analysis of two STBSG-EORTC phase III clinical trials

A. Le Cesne[1*], M. Ouali[2], M. G. Leahy[3], A. Santoro[4], H. J. Hoekstra[5], P. Hohenberger[6], F. Van Coevorden[7], P. Rutkowski[8], R. Van Hoesel[9], J. Verweij[10], S. Bonvalot[1], W. P. Steward[3], A. Gronchi[4], P. C. W. Hogendoorn[11], S. Litiere[2], S. Marreaud[2], J. Y. Blay[12] & W. T. A. Van Der Graaf[9]

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1. Le Cesne A, et al. Doxorubicin-based adjuvant chemotherapy in soft tissue sarcoma: pooled analysis of two STBSG-EORTC phase III clinical trials. Ann Oncol. 2014

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Adjuvant chemotherapy

- **No comprehensive answer**
- **Benefits appear to be more likely with:**
  - **High-grade STS**
  - **Regimens containing ifosfamide**
  - **Limb STS**

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Risk prediction in sarcoma

- **How to best identify patients at high risk of recurrence?**

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Risk prediction in sarcoma

- **MSKCC Postoperative Normogram**
  - **Estimates risk of sarcoma-specific death at 12-years**
    - **Size**
    - **Depth**
    - **Site of disease**
    - **Histology**
    - **Patient age**
    - **Grade of disease**
  - **Web-based calculator**

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1. Kattan MW, Leung DH, Brennan MF. Postoperative nomogram for 12-year sarcoma-specific death. J Clin Oncol. 2002 Feb 1;20(3):791-6.

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Risk prediction in sarcoma

- **SIN-system**
  - **Categorizes as high / low risk for metastasis-free survival**
    - **Tumor size > 8cm**
    - **Presence of vascular invasion**
    - **Microscopic tumor necrosis**
  - **Specific pathologic criteria**

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1. Gustafson P, et al. Prognostic information in soft tissue sarcoma using tumour size, vascular invasion and microscopic tumour necrosis-the SIN-system. Eur J Cancer. 2003 Jul;39(11):1588-95.

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Risk prediction in sarcoma

- **Sarculator**
  - **Estimates 5 and 10-year OS and risk of metastases in extremity STS**
    - **Patient age at diagnosis**
    - **Tumor size**
    - **Tumor depth**
    - **Surgical margin status**
    - **Tumor grade**
    - **Histological subtype**
  - **Updated to include primary/recurrent retroperitoneal STS**

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1. Callegaro D, et al. Development and external validation of two nomograms to predict overall survival and occurrence of distant metastases in adults after surgical resection of localized soft-tissue sarcomas of the extremities: a retrospective analysis. Lancet Oncol. 2016 May

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Risk prediction in sarcoma

Sarculator is a Good Model to Predict Survival in Resected Extremity and Trunk Sarcomas in US Patients

Rachel K. Voss, MD, MPH[1], Dario Callegaro, MD[2], Yi-Ju Chiang, MSPH[3], Marco Fiore, MD[2], Rosalba Miceli, PhD[2], Emily Z. Keung, MD[3], Barry W. Feig, MD[3], Keila E. Torres, MD, PhD[3], Christopher P. Scally, MD[3], Kelly K. Hunt, MD[3], Alessandro Gronchi, MD[2], and Christina L. Roland, MD, MS[3]

[1]Department of Sarcoma Oncology, H. Lee Moffitt Cancer Center, Tampa, FL; [2]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [3]Department of Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX

1. Voss RK, et al. Sarculator is a Good Model to Predict Survival in Resected Extremity and Trunk Sarcomas in US Patients. Ann Surg Oncol. 2022

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Neoadjuvant therapy

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Neoadjuvant chemotherapy: ISG-STS 1001

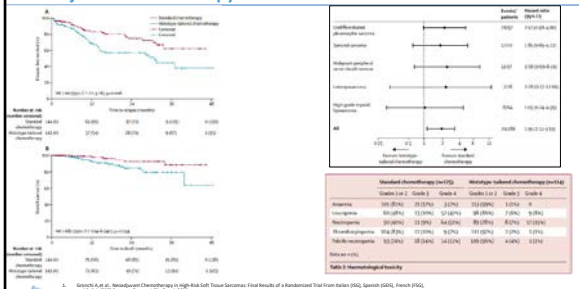
Neoadjuvant Chemotherapy in High-Risk Soft Tissue Sarcomas: Final Results of a Randomized Trial From Italian (ISG), Spanish (GEIS), French (FSG), and Polish (PSG) Sarcoma Groups

Alessandro Gronchi, MD[1]; Emanuela Palmerini, MD, PhD[2]; Vittorio Quagliuolo, MD[3]; Javier Martin Broto, MD, PhD[4,5]; Antonio Lopez Pousa, MD[6]; Giovanni Grignani, MD[7]; Antonella Brunello, MD, PhD[8]; Jean-Yves Blay, MD, PhD[9,10]; Oscar Tanchero, MD[11]; Robert Diaz Beveridge, MD, PhD[12]; Virginia Ferraresi, MD[13]; Iwona Lugowska, MD, PhD[14]; Domenico Franco Merlo, D.Phil[15]; Valeria Fontana, PhD, MSc[16]; Emanuela Marchesi, PhD, MSc[17]; Luca Braglia, MSc[18]; Davide Maria Donati, MD[19]; Elena Palassini, MD[19]; Giuseppe Bianchi, MD[19]; Andrea Manari, MD[20]; Carlo Morosi, MD[21]; Silvia Stacchiotti, MD[19]; Sibele Bagué, MD[22]; Jean Michel Coindre, MD[23]; Angelo Paolo Dei Tos, MD[24,25]; Piero Picci, MD[26]; Paolo Bruzzi, MD[16]; and Paolo Giovanni Casali, MD[16,27]

1. Gronchi A, et al. Neoadjuvant Chemotherapy in High-Risk Soft Tissue Sarcomas: Final Results of a Randomized Trial From Italian (ISG), Spanish (GEIS), French (FSG), and Polish (PSG) Sarcoma Groups. J Clin Oncol. 2020

60

Neoadjuvant chemotherapy: ISG-STS 1001 trial



	Standard chemotherapy (n=172)			Histotype-tailored chemotherapy (n=114)		
	Grades 1 or 2	Grade 3	Grade 4	Grades 1 or 2	Grade 3	Grade 4
Anaemia	101 (59%)	25 (15%)	2 (1%)	112 (100%)	1 (1%)	0
Leucopenia	84 (49%)	72 (42%)	17 (10%)	88 (78%)	7 (6%)	9 (8%)
Neutropenia	101 (60%)	33 (19%)	54 (32%)	85 (78%)	8 (7%)	17 (15%)
Thrombocytopenia	104 (61%)	17 (10%)	9 (5%)	101 (57%)	7 (6%)	5 (4%)
Febrile neutropenia	53 (34%)	18 (16%)	14 (12%)	109 (59%)	4 (4%)	1 (1%)

Data are n (%).

Table 3: Haematological toxicity

1. Gronchi A, et al.: Neoadjuvant Chemotherapy in High-Risk Soft Tissue Sarcomas: Final Results of a Randomized Trial From Italian (ISG), Spanish (GEIS), French (FSG), and Polish (PSG) Sarcoma Groups. J Clin Oncol. 2020
2. Gronchi A, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase II, multicentre trial. Lancet Oncol. 2017

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Neoadjuvant chemotherapy: ISG-STS 1001 trial

- **Issues**
  - **No control arm**
  - **Longer follow up (toxicity)**
  - **Differences in surgical techniques**
    - **32 hospitals across 4 countries**
- **Doxorubicin + ifosfamide (AIM) should remain standard in neoadjuvant**
- **Most benefit in sarculator OS < 60% in later pre-planned analysis**

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(Neo)Adjuvant chemotherapy: Approach at UNC

- **Risk-adapted approach**
  - **High risk for recurrence with surgery alone**
  - **Candidate for intensive chemotherapy**
  - **Chemotherapy-sensitive histology**
  - **In-depth discussion of limitations and unknowns in trial data**
- **Neoadjuvant favored over adjuvant, in most cases**

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Question #3

A 78 yo male with CAD notices progressive left thigh swelling and pain over the past 4 months. CT imaging from his PCP demonstrates a 9x12cm mass in the deep thigh involving the neurovascular bundle, and a round 2cm solitary right upper lobe nodule. A core needle biopsy of the thigh mass demonstrates leiomyosarcoma.

He is referred to you for treatment recommendations, and states he wants to "try something" for treatment but not "if it will make [him] really sick". Mild thigh discomfort is his only current symptom.

Exam: Thin, older male with enlargement of the left thigh. His gait is normal, and lungs are clear. PS is excellent.

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Metastatic STS

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Metastatic STS

- **1st line therapy, roughly 1980s-2000s:**
  - **Doxorubicin, or**
  - **Doxorubicin + ifosfamide (AIM)**

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Metastatic STS

Randomised phase II trial of pegylated liposomal doxorubicin (DOXIL®/CAELYX®) versus doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by the EORTC Soft Tissue and Bone Sarcoma Group

I. Judson[a,*], J.A. Radford[b], M. Harris[b], J.-Y. Blay[c], Q. van Hoesel[d], A. le Cesne[e], A.T. van Oosterom[f], M.J. Clemons[h], C. Kamby[g], C. Hermans[h], J. Whittaker[i], E. Donato di Paola[h], J. Verweij[j], S. Nielsen[k]

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1. Judson I, et al. Randomised phase II trial of pegylated liposomal doxorubicin (DOXIL/CAELYX) versus doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer. 2001 May

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Metastatic STS

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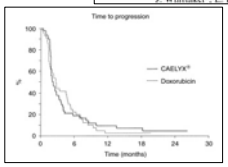

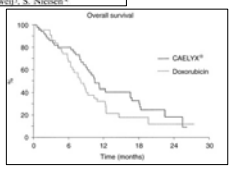

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Metastatic STS

Prognostic and predictive factors for outcome to first-line ifosfamide-containing chemotherapy for adult patients with advanced soft tissue sarcomas
An exploratory, retrospective analysis on large series from the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG)

Stefan Sleijfer [a,], Monia Ouali [b], Martine van Glabbeke [b], Anders Krarup-Hansen [c], Sjoerd Rodenhuis [d], Axel Le Cesne [e], Pancras C.W. Hogendoorn [f], Jaap Verweij [a], Jean-Yves Blay [g]*

70

1. Sleijfer S, et al. Prognostic and predictive factors for outcome to first-line ifosfamide-containing chemotherapy for adult patients with advanced soft tissue sarcomas: an exploratory, retrospective analysis on large series from the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG). Eur J Cancer. 2010 Jan

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Metastatic STS

Doxorubicin Plus Dacarbazine, Doxorubicin Plus Ifosfamide, or Doxorubicin Alone as a First-Line Treatment for Advanced Leiomyosarcoma: A Propensity Score Matching Analysis From the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group

Lorenzo D'Ambrosio, MD, PhD [1,2], Nathan Touati, PhD[3], Jean-Yves Blay, MD [4], Giovanni Grignani, MD [5], Ronan Flippot, MD[6], Anna M. Czarnecka, MD[7,8], Sophie Piperno-Neumann, MD[9], Javier Martin-Broto, MD[10], Roberta Sanfilippo, MD[11], Daniela Katz, MD[3], Florence Duffaud, MD[12], Bruno Vincenzi, MD[13], Daniel P. Stark, MD[14], Filomena Mazzeo, MD[15], Armin Tuschaserer, MD[16], Christine Chevreau, MD [17], Jenny Shenoff, MD[18], Anna Extival, MD[19], Saskia Litière, PhD[3], Ward Sente, PhD[3], Isabelle Ray-Coquard, MD, PhD[20], Francesco Tolomeo, MD[21], Axel Le Cesne, MD[3], Piotr Rutkowski, MD[8,7], Silvia Stacchiotti, MD [22], Bernd Kasper, MD [23], Hans Gelderblom, MD[24], and Alessandro Gronchi, MD [25], on behalf of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group

1. D'Ambrosio L, et al. Doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, or doxorubicin alone as a first-line treatment for advanced leiomyosarcoma: A propensity score matching analysis from the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Cancer. 2020 Jun

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Metastatic STS

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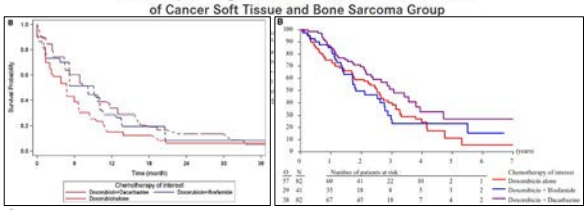

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Metastatic STS

Randomized Comparison of Pazopanib and Doxorubicin as First-Line Treatment in Patients With Metastatic Soft Tissue Sarcoma Age 60 Years or Older: Results of a German Intergroup Study

Viktor Grünwald, MD[1,2]; Annika Karch, MSc[2]; Markus Schuler, MD[3]; Patrick Schöffski, MD[4]; Hans-Georg Kopp, MD[5]; Sebastian Bauer, MD[6]; Bernd Kasper, MD, PhD[7]; Lars H. Lindner, MD[8]; Jens-Marcus Chemnitz, MD[9,10]; Martina Crysandt, MD[11]; Alexander Stein, MD[12]; Björn Steffen, MD[13]; Stephan Richter, MD[14]; Gerlinde Egerer, MD[15]; Philipp Ivanyi, MD[1]; Silke Zimmermann, MSc[11]; Xiaofei Liu, MSc[2]; and Annegret Kunitz, MD[16,17]

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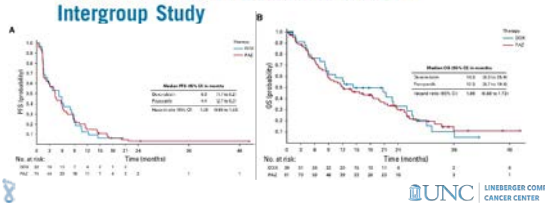
Metastatic STS

Randomized Comparison of Pazopanib and Doxorubicin as First-Line Treatment in Patients With Metastatic Soft Tissue Sarcoma Age 60 Years or Older: Results of a German Intergroup Study



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Metastatic STS

A phase II study of pazopanib as front-line therapy in patients with non-resectable or metastatic soft-tissue sarcomas who are not candidates for chemotherapy

Angela C. Hirbe[a,b,1], Vanessa Eulo[b,1], Chang I. Moon[c], Jingqin Luo[b,d], Stephanie Myles[a,b], Mahesh Seetharam[e], Jacqui Toeniskoetter[e], Tammy Kershner[e], Sasha Haarberg[e], Mark Agulnik[e], Varun Monga[f], Mohammad Milhem[e], Amanda Purkes[g], Steven Robinson[h], Scott Okuno[h], Steven Attia[i], Brian A. Van Tine[a,b,e]

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Metastatic STS

Effect of Doxorubicin Plus Olaratumab vs Doxorubicin Plus Placebo on Survival in Patients With Advanced Soft Tissue Sarcomas
The ANNOUNCE Randomized Clinical Trial

William D. Tap, MD; Andrew J. Wagner, MD, PhD; Patrick Schöffski, MD, PhD, MPH; Javier Martin-Broto, MD, PhD; Anders Kransp-Hansen, MD, PhD; Kristen N. Ganjoo, MD; Chueh-Chuan Yen, MD; Albiruni R. Abdul Razak, MRCPI; Alexander Spira, MD, PhD; Akira Kawai, MD, PhD; Axel Le Cesne, MD; Brian A. Van Tine, MD, PhD; Yoichi Naito, MD; Se Hoon Park, MD, PhD; Alexander Fedenko, MD; Zsuzsanna Papai, MD, PhD; Victoria Soldatenkova, MS; Ashwin Shahir, MD; Gary Mo, PhD; Jennifer Wright, MD; Robin L. Jones, MD, MBBS, BSc; for the ANNOUNCE Investigators

76 1. Tap WD, et al. Effect of Doxorubicin Plus Olaratumab vs Doxorubicin Plus Placebo on Survival in Patients With Advanced Soft Tissue Sarcomas: The ANNOUNCE Randomized Clinical Trial. JAMA. 2020 Apr 7

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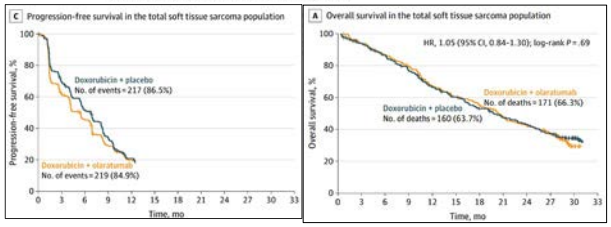
Metastatic STS

Effect of Doxorubicin Plus Olaratumab vs Doxorubicin Plus Placebo on Survival in Patients With Advanced Soft Tissue Sarcomas
The ANNOUNCE Randomized Clinical Trial



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Metastatic STS

- **1st line therapy:**
  - **Doxorubicin, or**
  - **Doxorubicin + ifosfamide (AIM)**
  - **Doxorubicin + dacarbazine in LMS?**
  - **Liposomal doxorubicin**
  - **Pazopanib**

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Metastatic STS: Approach at UNC

1. Patient's goals, symptoms and expectations

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Metastatic STS: Approach at UNC

1. Patient's goals, symptoms and expectations
2. QoL with ongoing and future therapy

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Metastatic STS: Approach at UNC

1. Patient's goals, symptoms and expectations
2. QoL with ongoing and future therapy
3. Multidisciplinary care

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Metastatic STS: Approach at UNC

1. Patient's goals, symptoms and expectations
2. QoL with ongoing and future therapy
3. Multidisciplinary care
4. Navigating changes in goals of care

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Metastatic STS: Immunotherapy

Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial

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Metastatic STS: Immunotherapy

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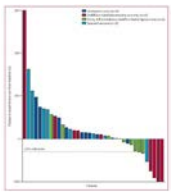

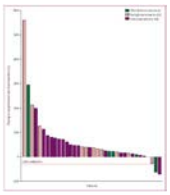

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Metastatic STS: Immunotherapy

Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single-arm, phase 2 trial

Brevlyn A Wilky, Matteo M Trucco, Ty K Subhawong, Vasa Florou, Wungki Park, Dewhwan Kwon, Eric D Wieder, Dingxia Kolanian, Andrew E Rosenberg, Darcy A Kerr, Efterpiri Sjaklavanakis, Mark Foley, Jaime R Merchan, Krishna V Komanduri, Jonathan C Trent

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Metastatic STS: Immunotherapy

Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single-arm, phase 2 trial

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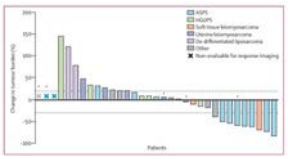

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Metastatic STS: Immunotherapy

Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials

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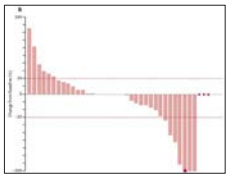
Metastatic STS: Immunotherapy

Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials



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Metastatic STS: Immunotherapy

- SARC028
  - n=40, STS
  - ORR 18%
- Alliance A091401
  - n=85, bone + STS
  - ORR: 16% with ipi + nivo, 5% with nivo
    - Expansion cohorts for DDLPS and UPS
      - ORR 4/24 with ipi + nivo
      - ORR 2/24 with nivo
- Wilky, et al MDACC
  - n=33, n=21 for non ASPS
  - 2/21 with pembrolizumab + axitinib
- Somaiah, et al MDACC
  - n=56, STS + ASPS
  - Similar findings with durvalumab + tremelimumab

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Metastatic STS: Immunotherapy

- **Benefits greatest in certain subtypes**
  - **ASPS**
  - **UPS**
  - **ddLPS**
- **Biomarkers needed**
- **PD1 vs. PDL1 + CTLA4 vs. PD1 + TKI**

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Summary

1. Workup and staging of STS can be straightforward, be aware of high-risk subtypes and situations that warrant early referrals
1. Adjuvant and neoadjuvant therapy for STS remains case-by-case
1. Newer data offers therapy for frailer patients with metastatic disease
1. Immunotherapy is not widely utilized outside of specific sarcoma subtypes

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Jake Stein (Medical oncology)
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John Tobben, Daniel Nissman (Radiology, MSK imaging)
Leslie Dodd, Bart Singer, Laleh Hakima (Pathology)
Stephanie Shea (Adult sarcoma nurse navigator)
Kevin Chen (Adult sarcoma clinical pharmacist)
UNC AYA Cancer program:
Lauren Lux, Andrew Smitherman, Melissa Matson, Catherine Swift

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Questions/Comments?

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Nadja Brown, Interim Administrative Support Specialist
Patrick Muscarella, Technology Support Technician
Lauren Lowe, Intern

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UPCOMING LIVE WEBINARS

PATIENT CENTERED CARE
August 9
12:00 PM
Cognitive Dysfunction in Patients with Cancer
Zev Nakamura, MD

ADVANCED PRACTICE PROVIDER
August 16
4:00 PM
Exercise and Wellness as Part of the Cancer Experience
Carly Bailey, MA

RESEARCH TO PRACTICE
August 23
12:00 PM
Head and Neck Cancer Management in North Carolina: Updates for 2023
Wendell Yarbrough, MD, MMHC, FACS
Siddharth Sheth, DO, MPH
Colette J. Shen, MD, PhD

Complete details on upcoming Live Webinars: learn.uncicn.org/live-webinars

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SELF-PACED, ONLINE COURSES

ADVANCED PRACTICE PROVIDER
Parenting with Cancer
Justin Michael Yopp, PhD

RESEARCH TO PRACTICE
The Ketogenic Diet for Brain Tumor Patients: A Phase 1 Trial and Beyond...
Jethro L. Hu, MD

PATIENT CENTERED CARE
Cancer Pathology: How Pathology Drives Treatment
Yuri Fedoriw, MD

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