Advances in Sarcoma: Focus on Clinical Trials

DATE: March 18, 2022

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Disclosures

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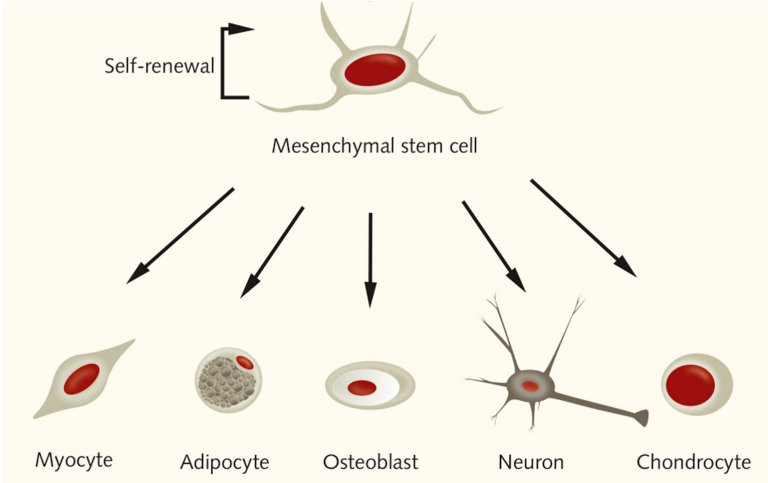
Background

- A heterogenous group of rare cancers
- 20% of pediatric cancers, 1% of adult cancers
- ~50% occur in AYAs
- Arise from mesenchymal cells; *distinct from carcinomas*



Sarcomas can arise in ANY part of the body at ANY age.

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Background

- **Soft tissue sarcomas**
  - GIST (4,000/yr)
  - Leiomyosarcoma (3,000/yr)
  - Liposarcoma (2,500/yr)
  - Undifferentiated sarcomas (2,500/yr)
  - plus ~100 other subtypes
- **Bone sarcomas**
  - Chondrosarcoma (1,400/yr)
  - Osteosarcoma (1,000/yr)
  - Ewings sarcoma (600/yr)
  - Chordoma (400/yr)

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Clinical Practice Guidelines

- ESMO–EURACAN–GENTURIS:
  - Management of STSs should be carried out in sarcoma reference centres or tertiary paediatric oncology centres as appropriate for age [III, A].
  - Pathological diagnosis should be made by a sarcoma expert pathologist according to the 2020 WHO classification [IV, A].
- NCCN:
  - Before treatment initiation, all patients should be evaluated and managed by a multidisciplinary team with extensive expertise and experience in the treatment of STS.

Treatment at low-volume centers is associated with worse outcomes.

Keung 2018; Bargaria 2018; Venigalla 2018; Lazarides 2019; Martin-Broto 2019; Blay 2019; Malik 2020; Eastman 2021; Blay 2022 etc

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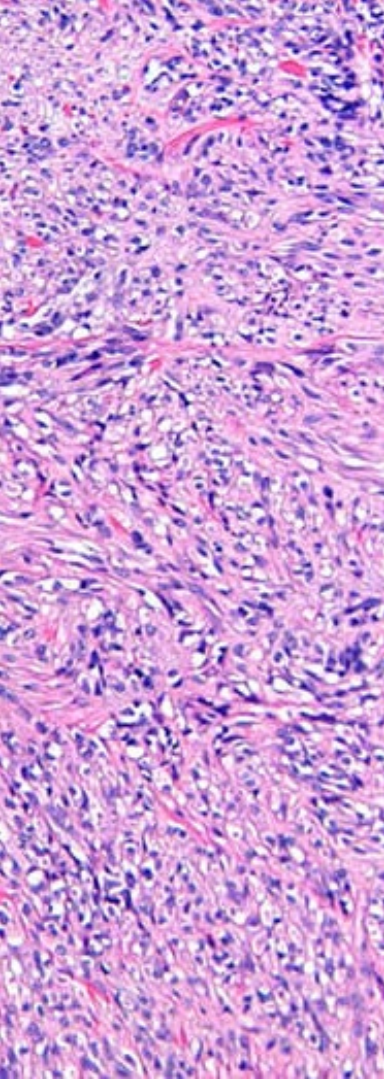
GIST



Advanced GIST

- THE-630
  - Phase 1/2 for any KIT or PDGFRA mutant GIST with at least 1 prior line of therapy (NCT05160168)
- Peak: Phase 3 Randomized Trial of CGT9486 + Sunitinib vs. Sunitinib
  - Phase 3 for KIT or PDGFRA mutant (excluding PDGFRA D842V) with imatinib-resistance/intolerance and sunitinib naïve (NCT05208047)
- Phase 2 of Temozolomide for SDH-deficient GIST (NCT03556384)
- Ripretinib + repaglinide drug-drug interaction study (NCT04530981)
  - At least 2 prior lines of TKI therapy

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Systemic Treatment of Advanced Soft Tissue Sarcoma: Current Status

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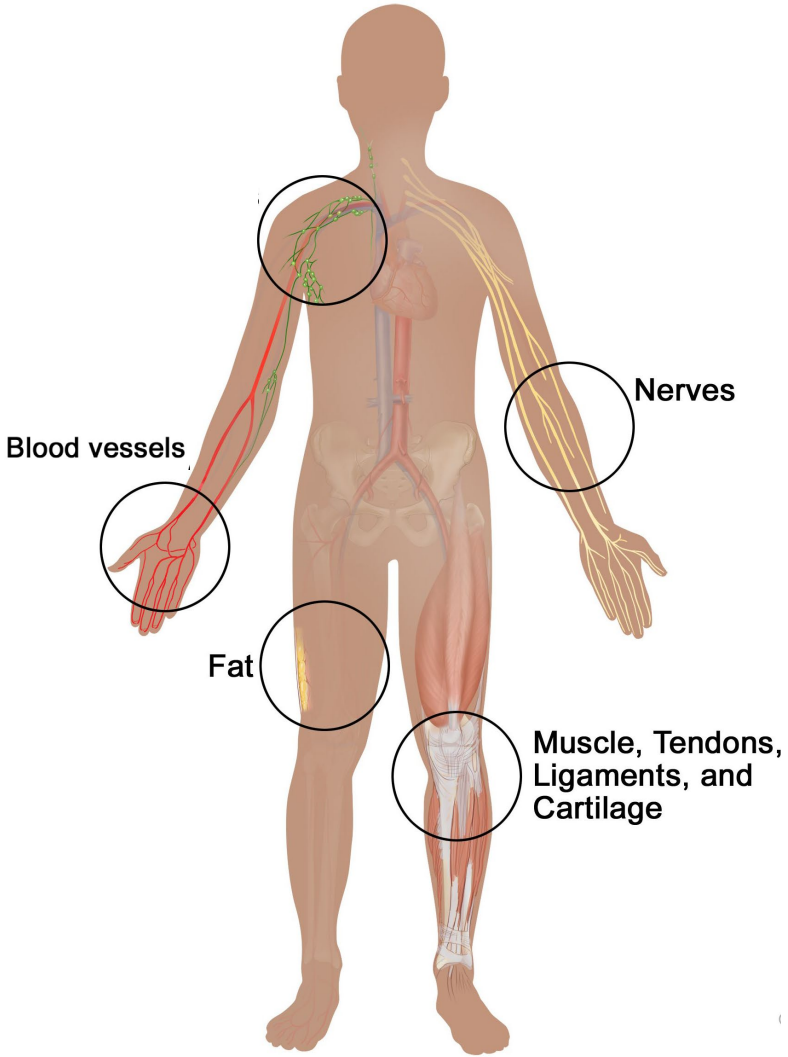

Soft Tissue Sarcomas (STS)

- Massive diversity in pathogenesis, cell of origin, histology, clinical behavior.
- Historically, there has been little diversity in treatment.

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Advanced STS

- Steady improvement in median overall survival
  - EORTC, 2014 (n=228) = 12.8 months
  - PICASSO trial, 2016 (n=221) = 16.9 months
  - GeDDiS trial, 2017 (n=129) = 17.7 months
  - TH-302 trial, 2017 (n=323) = 19.0 months
  - ANNOUNCE trial, 2020 (n=251) = 19.7 months

- 5yr overall survival = 10-15% (SEER)

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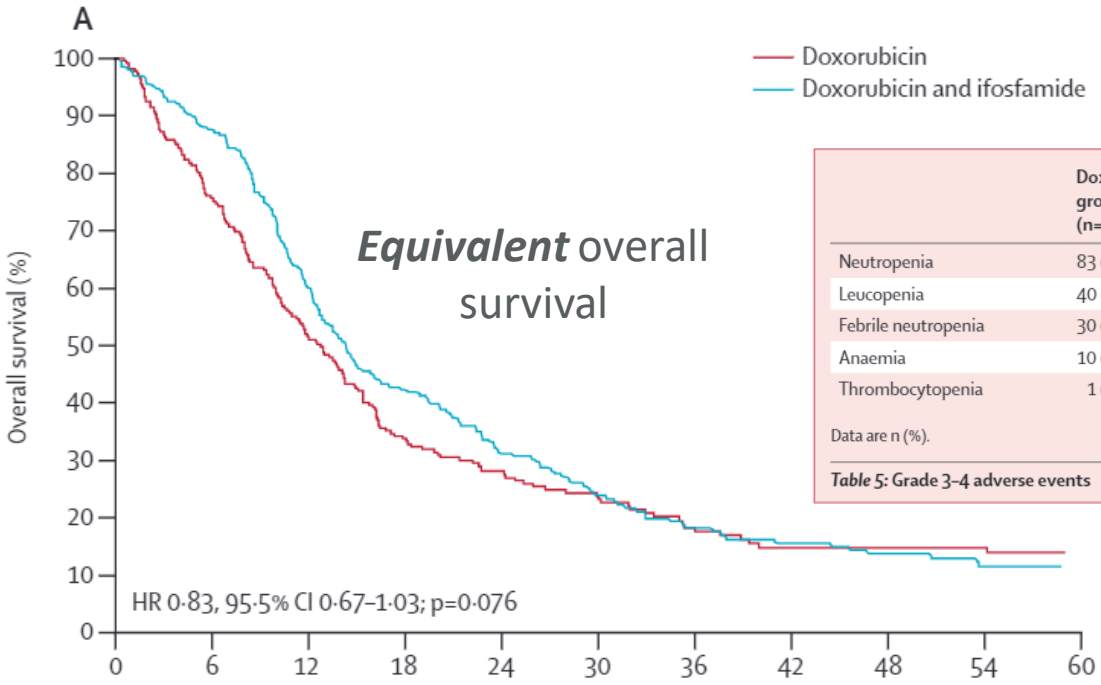
Advanced STS



Equivalent overall survival

	Doxorubicin group (n=223)	Doxorubicin and ifosfamide group (n=224)
Neutropenia	83 (37%)	93 (42%)
Leucopenia	40 (18%)	97 (43%)
Febrile neutropenia	30 (13%)	103 (46%)
Anaemia	10 (4%)	78 (35%)
Thrombocytopenia	1 (<1%)	75 (33%)

Data are n (%).

Table 5: **Grade 3–4 adverse events**

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Judson et al, Lancet Oncol, 2014

Systemic therapy progress: FDA drug approvals

1973
Doxorubicin

2012
Pazopanib

2016
Eribulin

2020
Tazemetostat

1980 … 1990 … 2000 … 2010

Used “off-label” for sarcomas: ifosfamide, etoposide, dacarbazine, gemcitabine, docetaxel, dactinomycin, vincristine, many others

2015
Trabectedin

2017
Olaratumab

2021
Nab-sirolimus

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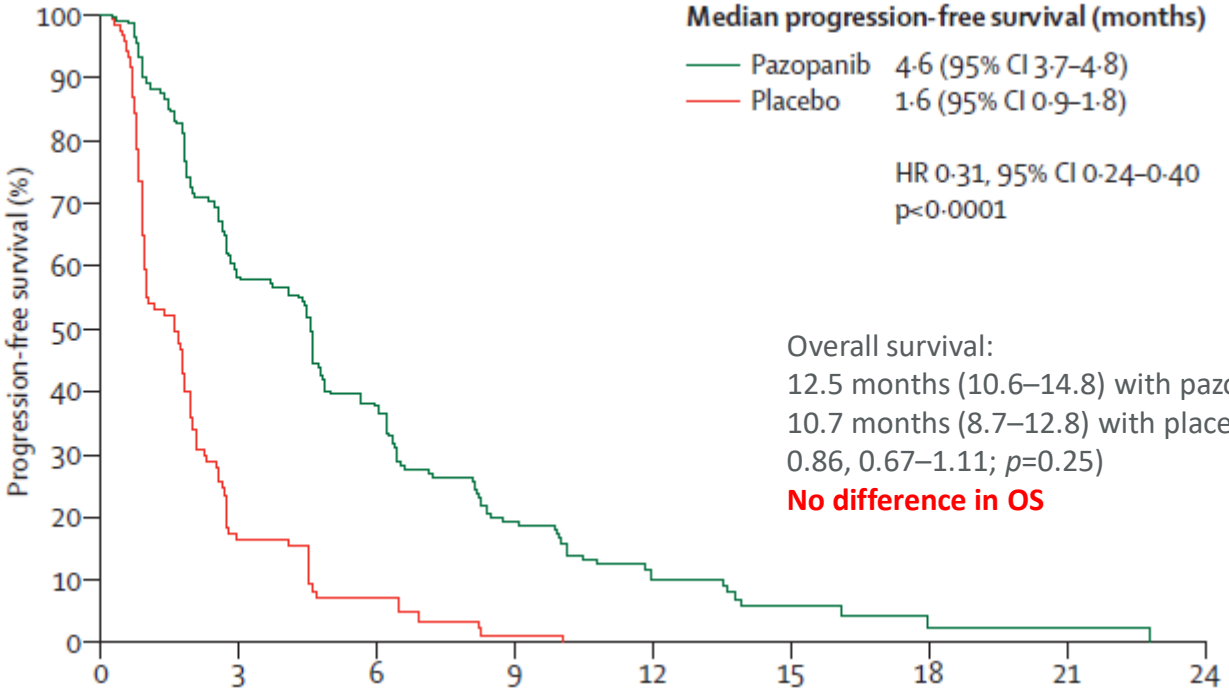
Pazopanib / Any Subtype STS



Overall survival:
12.5 months (10.6–14.8) with pazopanib vs 10.7 months (8.7–12.8) with placebo (HR 0.86, 0.67–1.11; *p*=0.25)
No difference in OS

FDA approved Apr 2012

PALETTE - Van der Graaf 2012 Lancet

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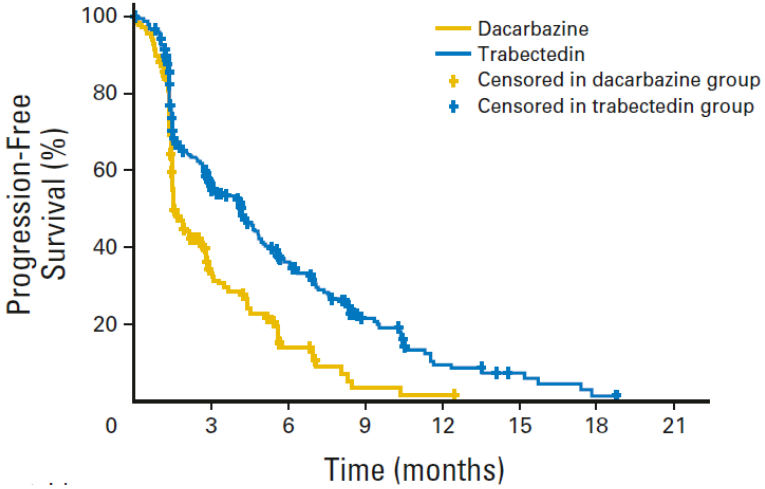
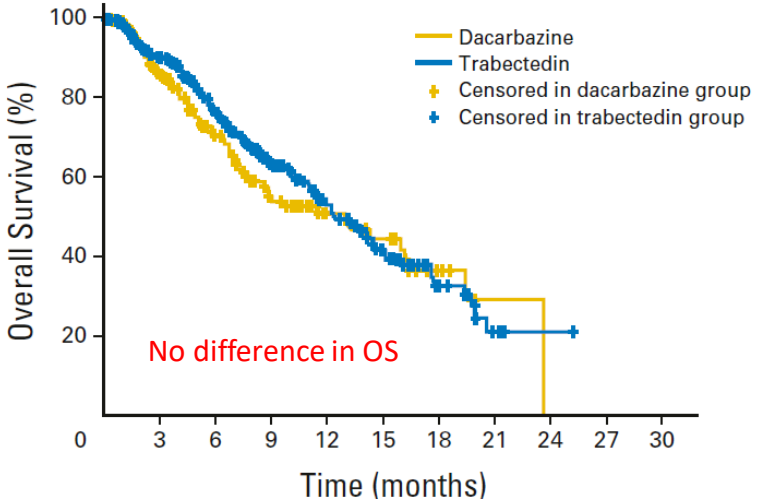
Trabectedin / Liposarcoma & Leiomyosarcoma





FDA approved Oct 2015

Demetri 2015 JCO

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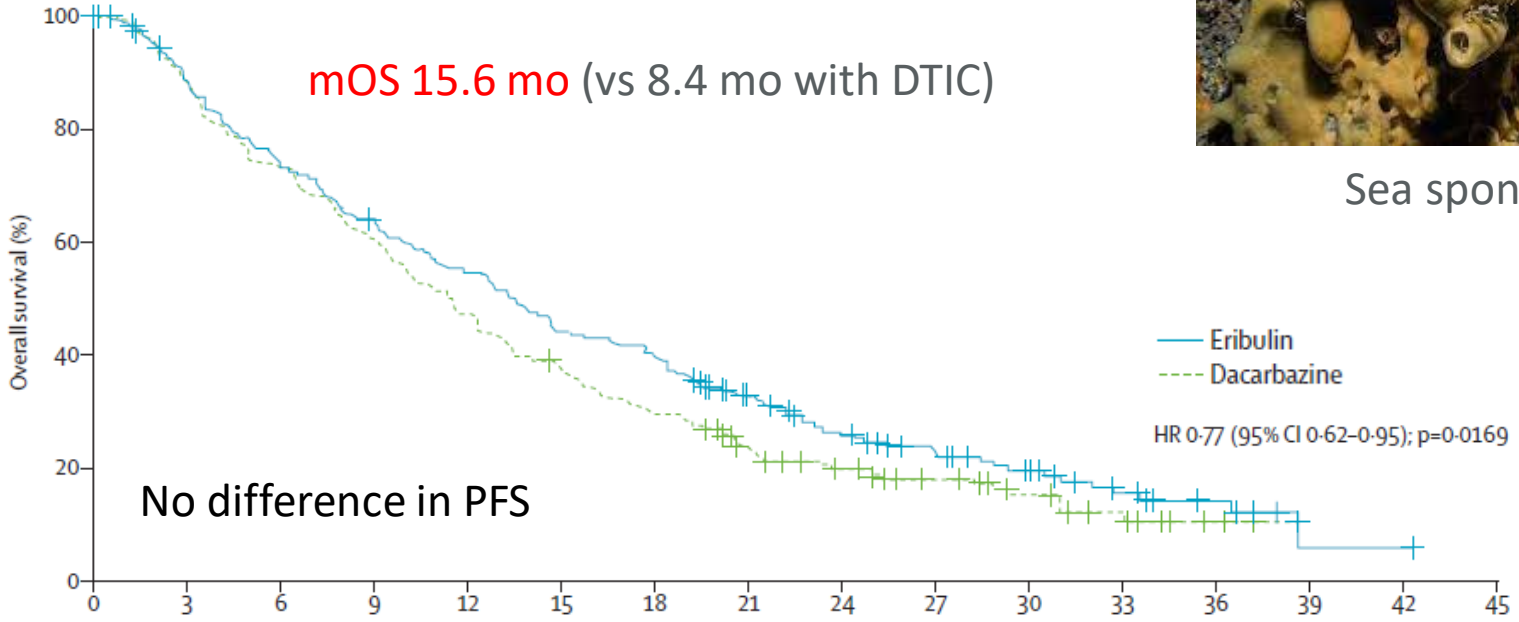
Eribulin / Liposarcoma

Sea sponge

mOS 15.6 mo (vs 8.4 mo with DTIC)



No difference in PFS

FDA approved Jan 2016

Schoffski 2016 Lancet

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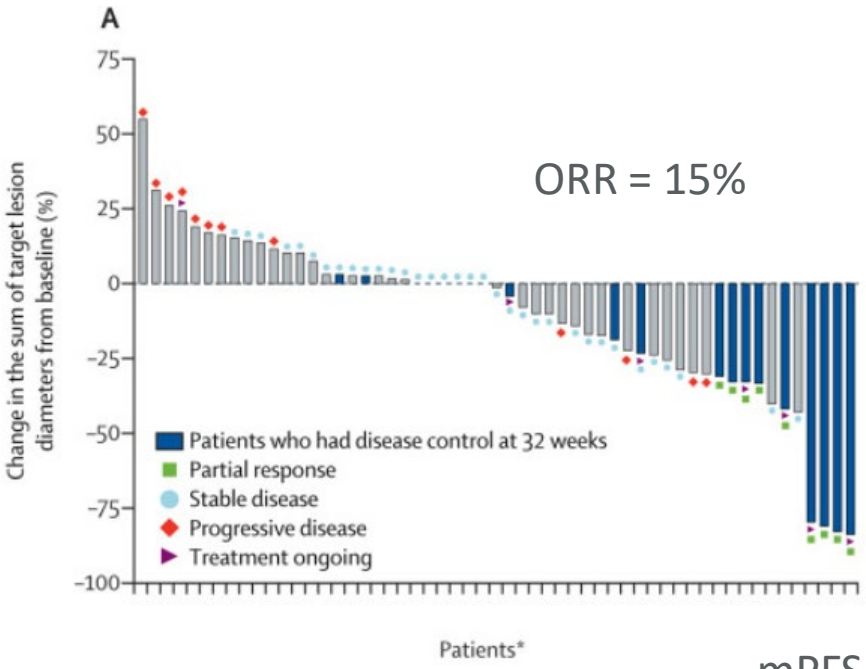
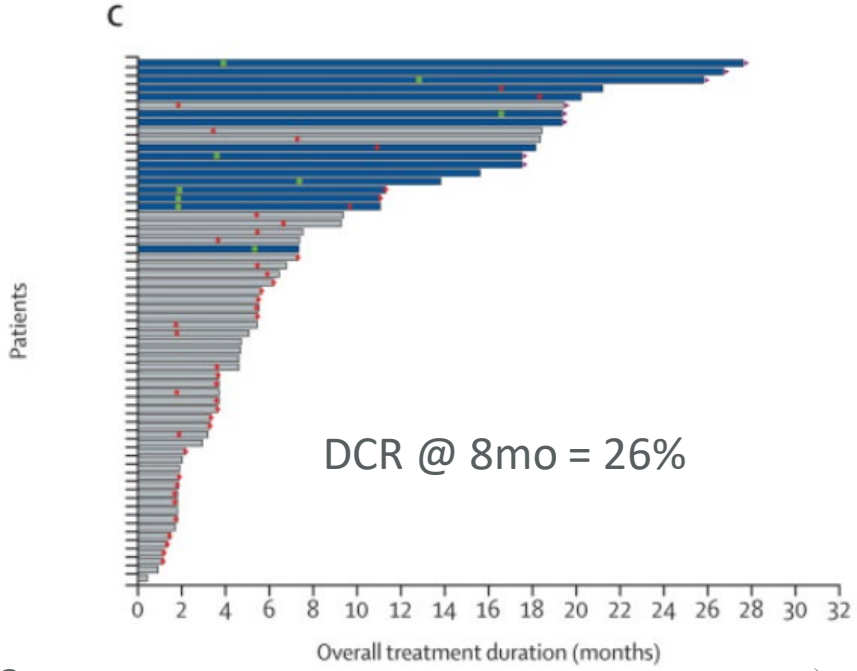
Tazemetostat / Epithelioid Sarcoma



ORR = 15%



DCR @ 8mo = 26%

mPFS = ~6mo
mOS = ~1.5y

FDA approved Jan 2020

Gounder et al, Lancet Oncol 2020

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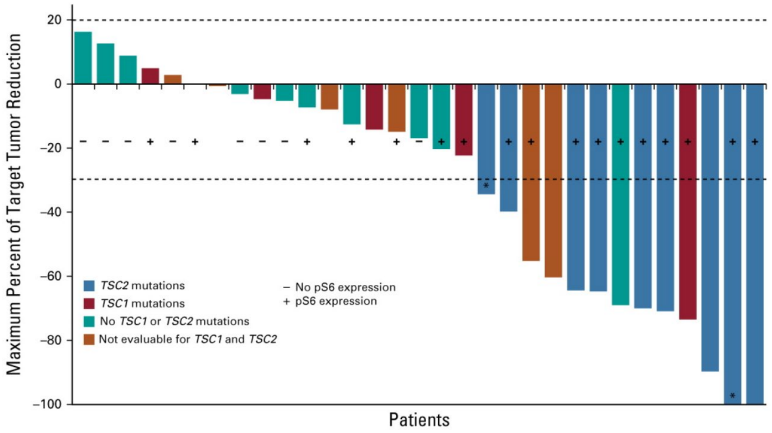
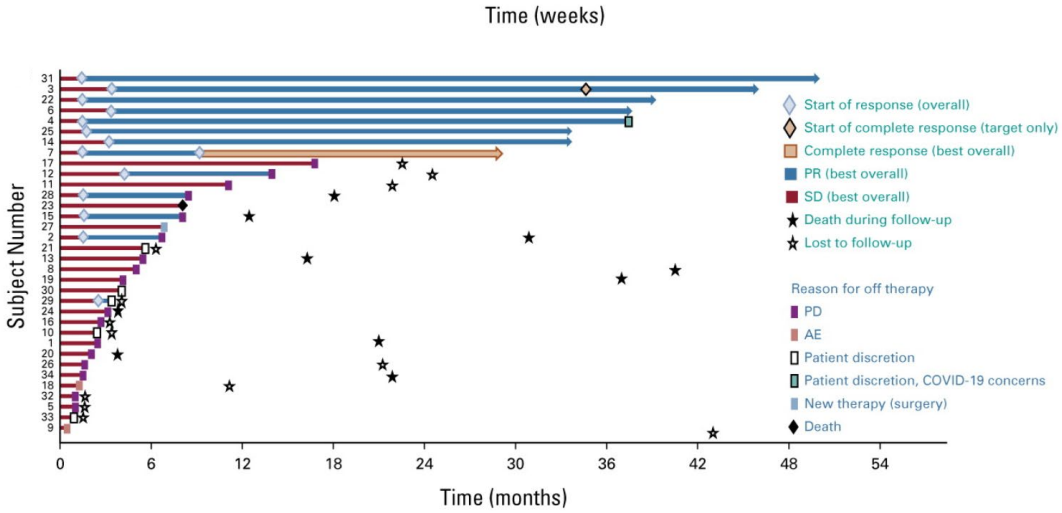
ASCO 2019

Nab-sirolimus / PEComa





mPFS = ~11mo

mOS = ~3.5y

FDA approved Nov 2021

Wagner 2021 JCO

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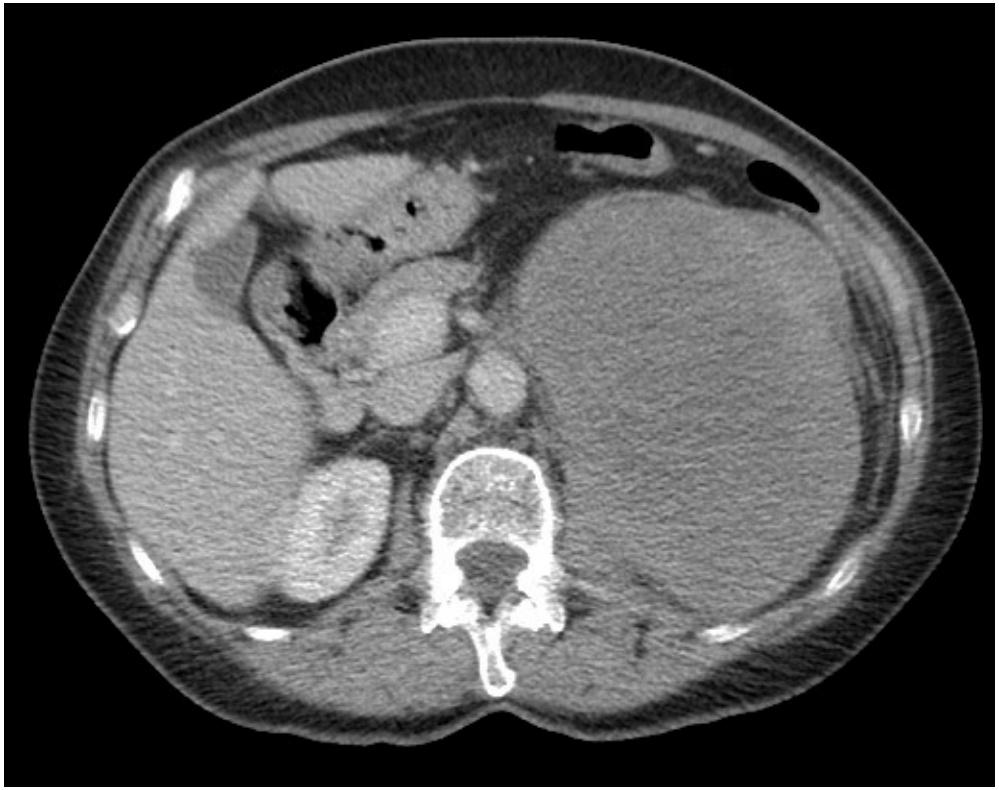
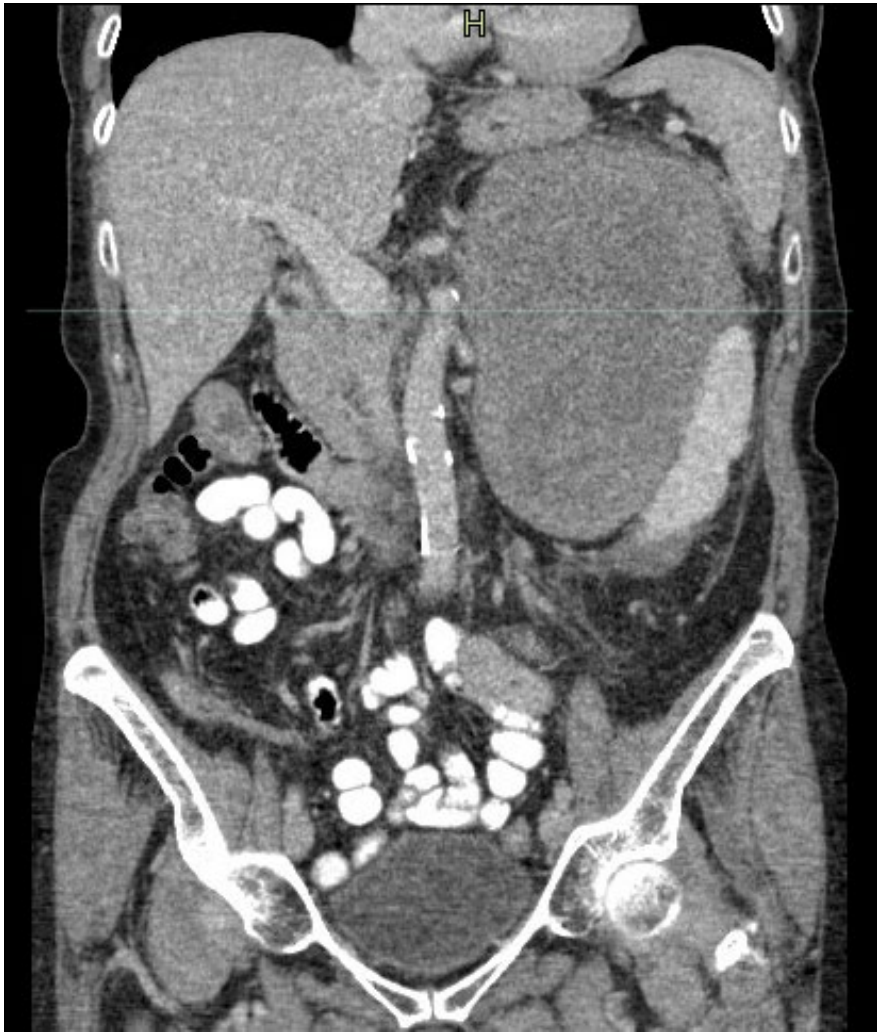
Subtype-Specific Studies: Liposarcoma

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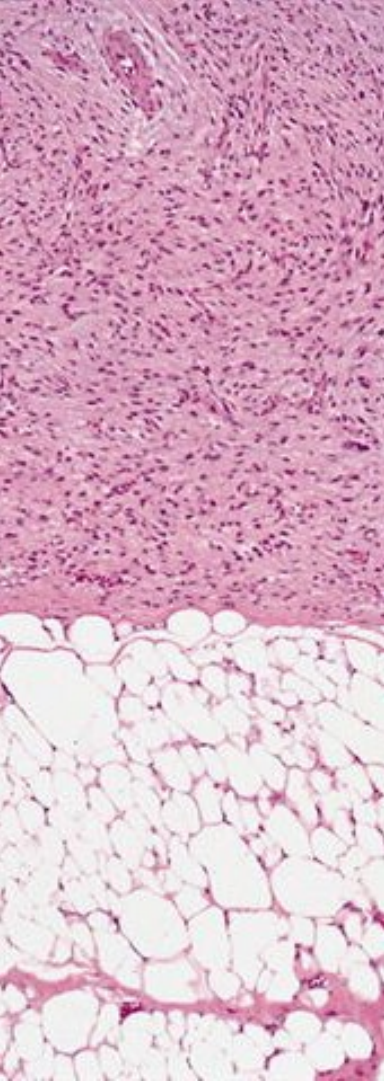

Retroperitoneal liposarcoma

Primary retroperitoneal sarcoma

Sarculator

- Age = 63 yr
- Tumor size = 18 cm
- Grade = 3
- Histology = Dediff liposarcoma
- Multifocality = No
- Complete resection = Yes

7-year OS = 34%

7-year DFS = 14%

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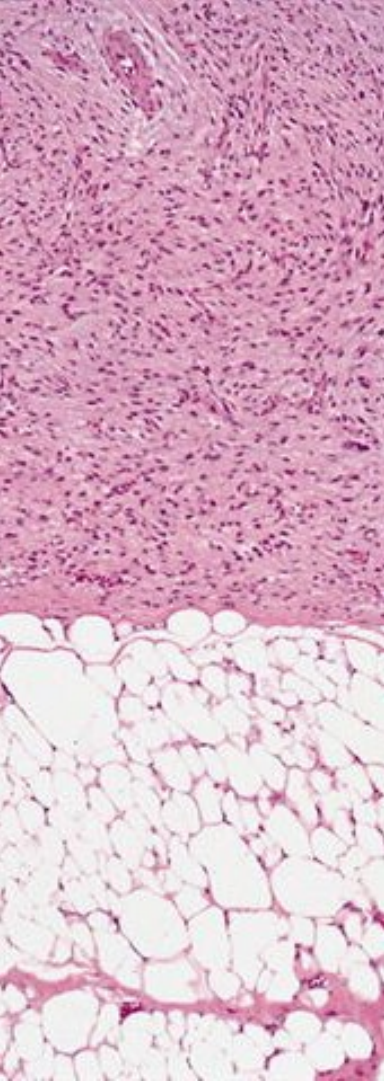

Retroperitoneal liposarcoma

- Standard of care = surgery only

- Consider a clinical trial of neoadjuvant chemoradiotherapy:
  - NCT03361436: *Eribulin and Radiation Therapy in Treating Patients With Retroperitoneal Liposarcoma That Can Be Removed by Surgery*

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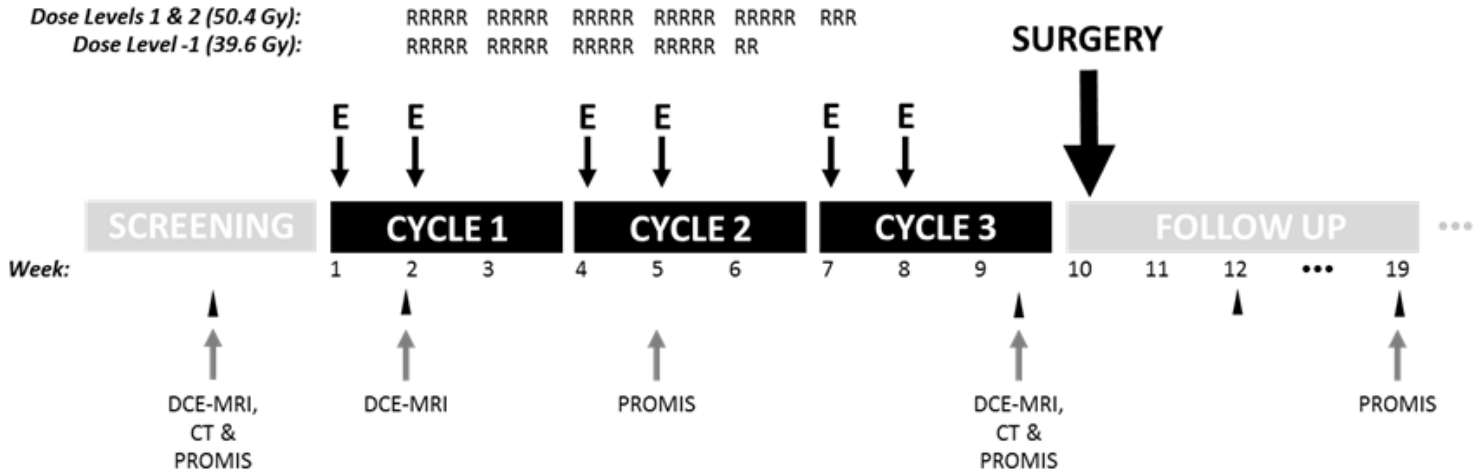
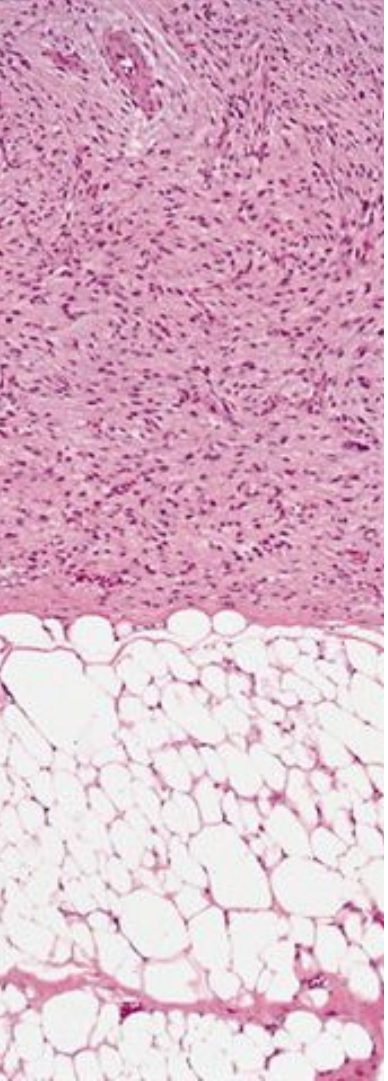


R = IMRT fraction of 1.8 Gy
E = Eribulin IV
DCE-MRI = Dynamic Contrast-Enhanced MRI
PROMIS = Patient- Reported Outcomes Measurement Information System questionnaires
▲ = research blood sample

Dose Level	Dose	
	Radiation (Gy)	Eribulin (mg/m^2)
Level 2	50.4	1.4
Starting Dose (Level 1)	50.4	1.1
Level -1	39.6	1.1

Main Criteria for Inclusion & Exclusion: Subjects with primary or recurrent retroperitoneal liposarcoma of any subtype will be eligible. The tumor must be deemed resectable with acceptable morbidity and targetable with intensity-modulated radiation therapy (IMRT) with acceptable morbidity. Eligible subjects will have no evidence of distant metastases, and will have no history of prior radiation or chemotherapy for their sarcoma.



Advanced liposarcoma

- **SARC041**: Study of Abemaciclib Versus Placebo in Patients With Advanced Dedifferentiated Liposarcoma (NCT04967521, 1+ line, randomized phase 3)

- **Brightline-1**: A Study to Compare BI 907828 (oral MDM2 inhibitor) With Doxorubicin in Dedifferentiated Liposarcoma (NCT05218499, 1st line, randomized phase 2/3)

- **MANTRA**: Treatment of Milademetan (oral MDM2 inhibitor) Versus Trabectedin in Patient With Dedifferentiated Liposarcoma (NCT04979442, 2+ line, randomized phase 3)

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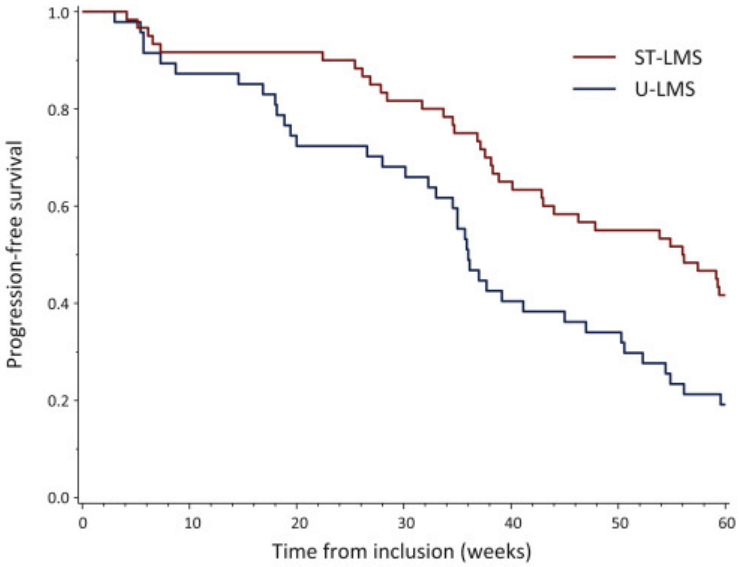
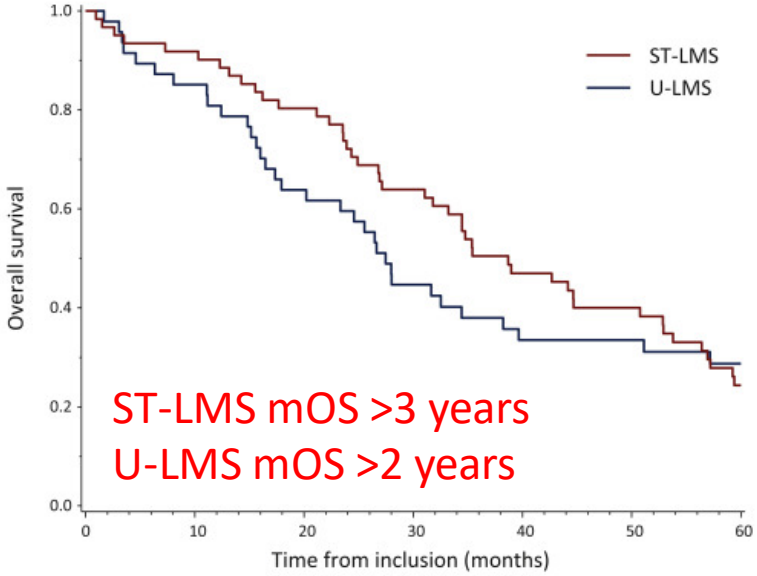
Subtype-Specific Studies: Leimyosarcoma

Advanced leiomyosarcoma

Aggressive first-line treatment with doxorubicin + trabectedin





Pautier 2021 ESMO Open

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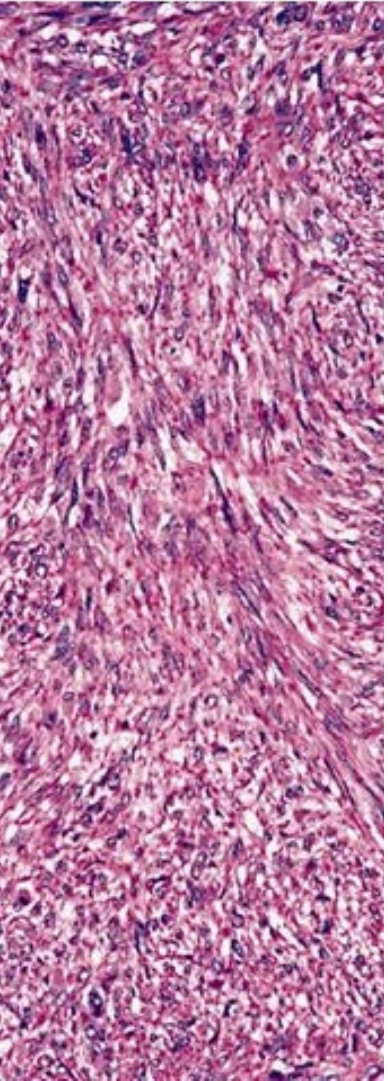
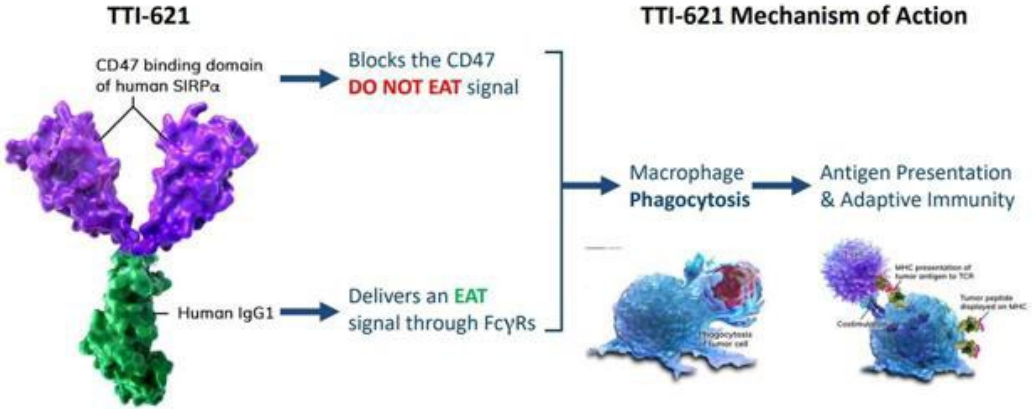


Advanced leiomyosarcoma

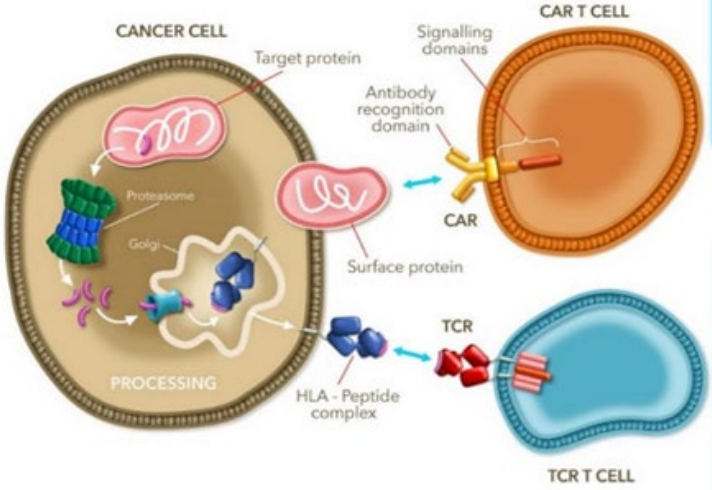
- TTI-621 in Combination with Doxorubicin in Patients with Unresectable or Metastatic High-Grade Leiomyosarcoma (NCT04996004, anthracycline naïve 1st or 2nd line, phase 1/2)



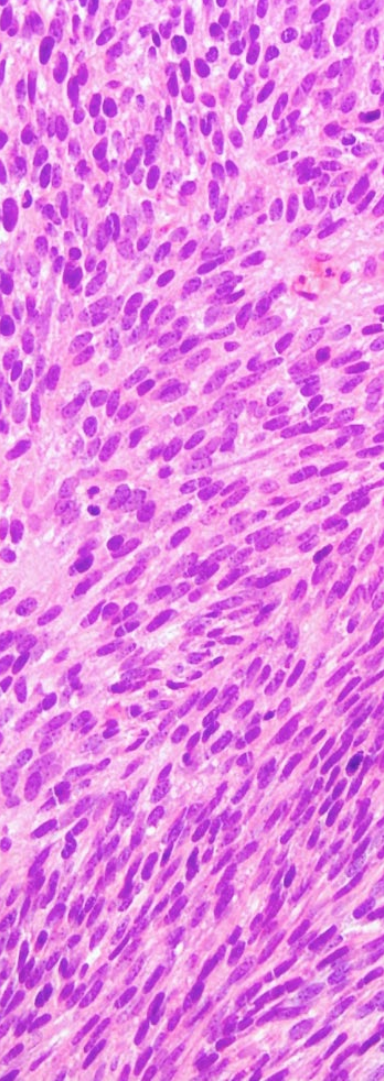
https://seekingalpha.com/article/4318351-trillium-therapeutics-under-new-management-and-advancing-dual-cdminus-47-targets

Cell therapy for sarcoma

T-cell therapy for sarcoma



CAR-T	Very few targets; limited to extracellular
	Chimeric antigen receptor; not designed to recognize an HLA peptide
TCRs	Access to extra- and intracellular proteins
	Affinity enhanced SPEAR TCRs overcome naturally low affinity target expression
	Requires MHC-I expression and HLA matching



Advanced synovial sarcoma (SS) & myxoid liposarcoma (MRCLS)

- IGNYTE-ESO: Genetically Engineered T Cells (Lete-cel) in NY-ESO-1 Positive Solid Tumors (NCT03967223, 1+ line, phase 2)

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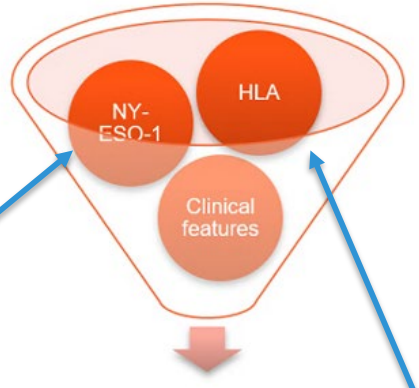
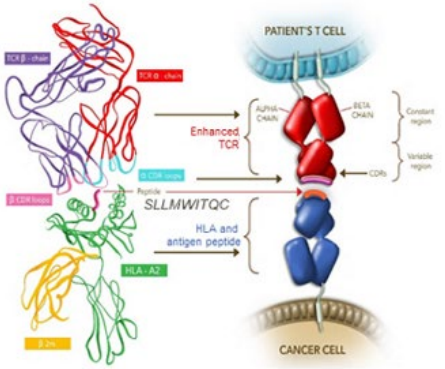
Lete-cel for SS & MRCLS



>50% synovial sarcomas

>90% myxoid LPS

Patient Screening Eligibility



GSK 3377794
Made for each patient
Not "off the shelf"

50% Caucasians
35% African Americans

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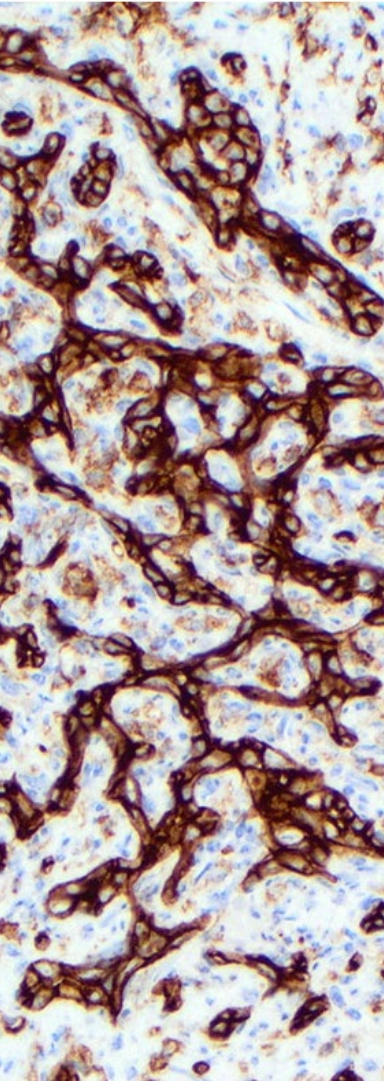
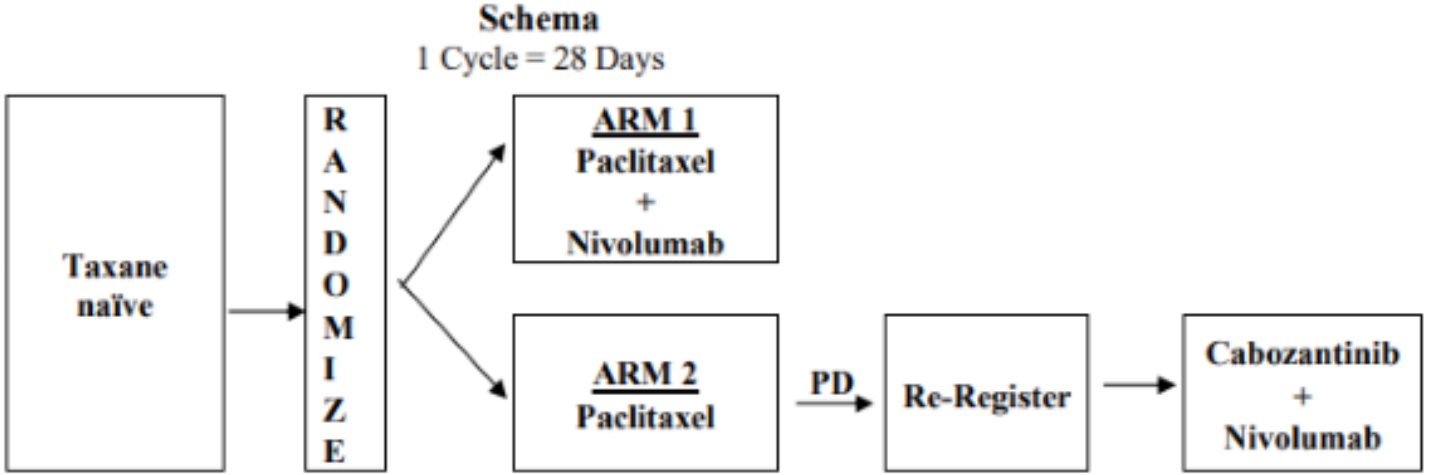
National Clinical Trials Network



Alliance A091902: Phase 2 of chemotherapy ± nivolumab for advanced angiosarcoma



NCT04339738

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High risk extremity Soft Tissue Sarcomas (STS)

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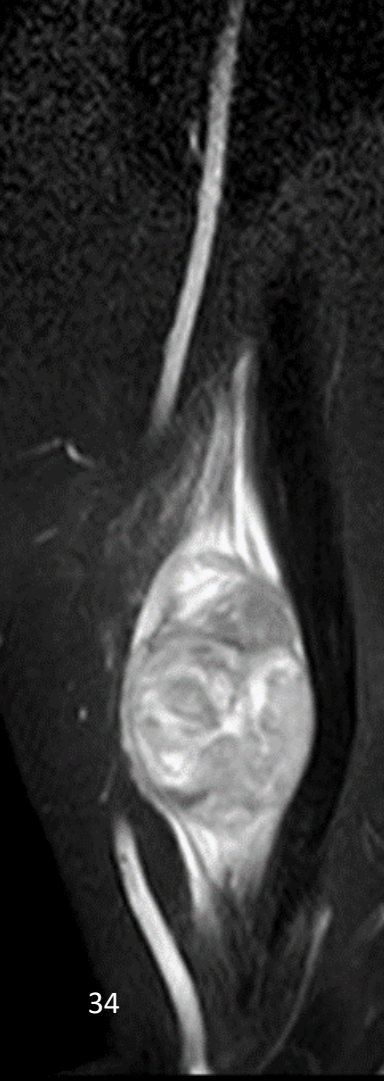

Localized STS

1. Surgery
   - Almost ALWAYS
   - By a surgical or orthopedic oncologist
   - Negative margin essential
2. Radiation
   - Definitely for large, high-grade sarcomas or positive margins
   - Pre- or post- op (different risks)

Open now: Phase III Study of Preoperative vs Postoperative IMRT For Truncal/Extremity Soft Tissue Sarcoma (NCT02565498)

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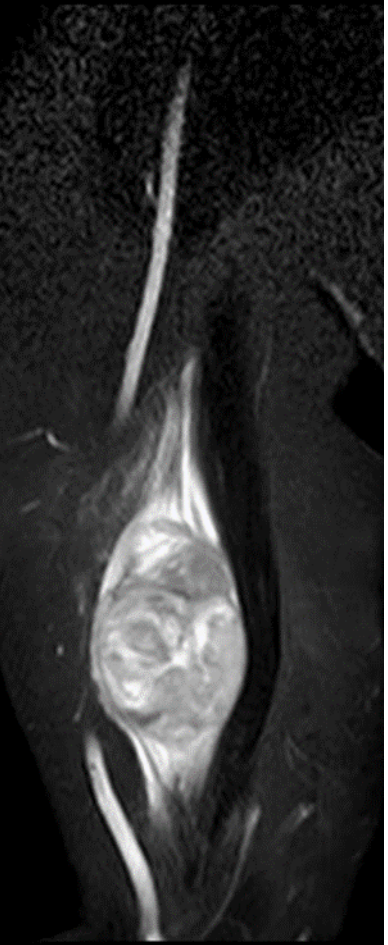

Localized STS

3. Chemotherapy?
   - Repeated randomized prospective trials have tested perioperative chemotherapy (eg, EORTC 62931) with no proven overall survival benefit.
   - Appropriate patient selection is the key!
     - Large, grade III, truncal/extremity tumors are the most likely to benefit from adjuvant AIM.

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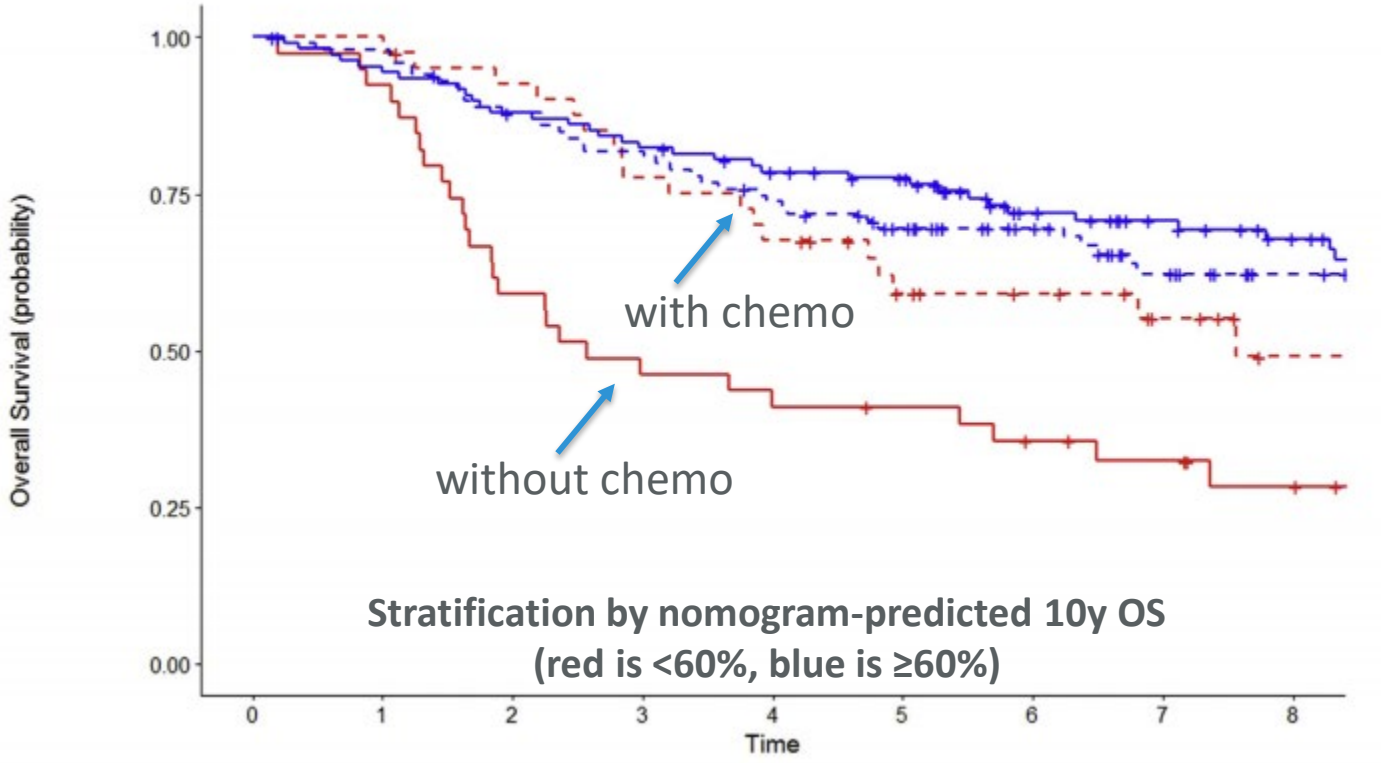
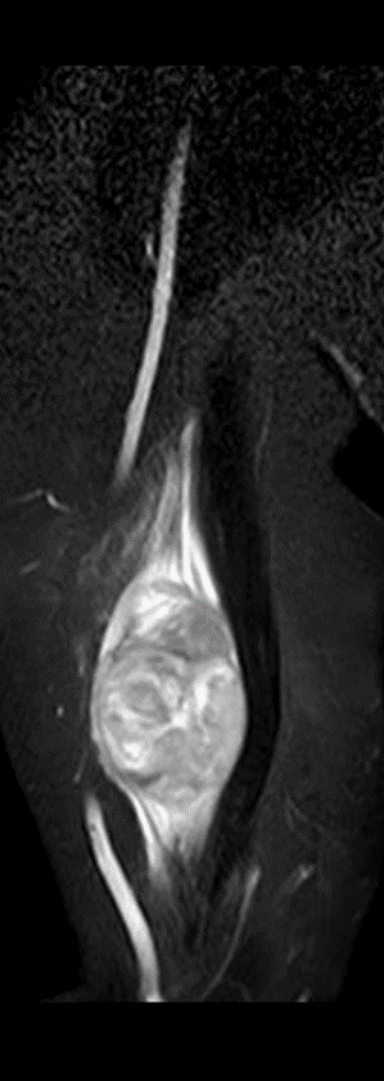
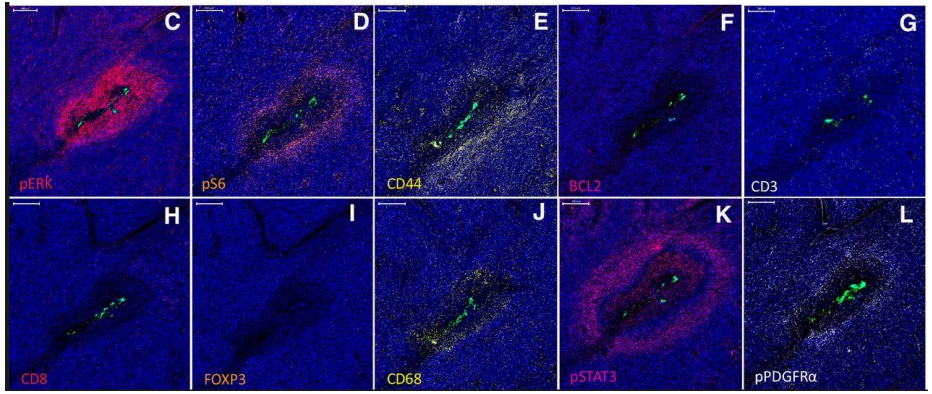


In this analysis of EORTC 62931, there is a **statistically significant reduction of the risk of death** when adjuvant chemotherapy was used in patients with low predicted survival (**HR = 0.50**, 95% CI 0.30-0.90)



Localized STS

- CIVO Intratumoral Microdosing of Anti-Cancer Therapies (NCT04541108)



- SAFETY: Surveillance AFter Extremity Tumor surgerY (NCT03944798)
  - Randomized trial comparing surveillance frequency (q3 vs. q6 months) and imaging modality (CT vs. CXR)

Gundle 2020

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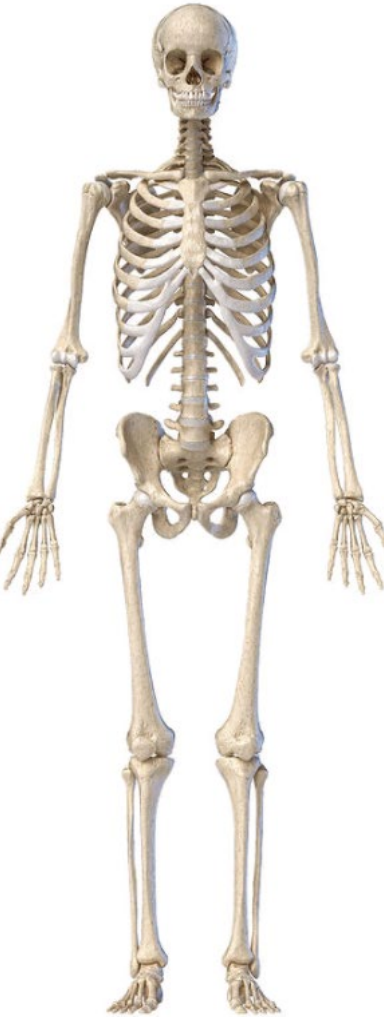
Bone Sarcomas



Bone Sarcomas

- Chemotherapy is well established as ***essential*** to the treatment of osteosarcoma and Ewings sarcoma.
- Osteosarcoma & Ewings sarcoma are ***curable*** with multi-agent, multi-modality therapy.

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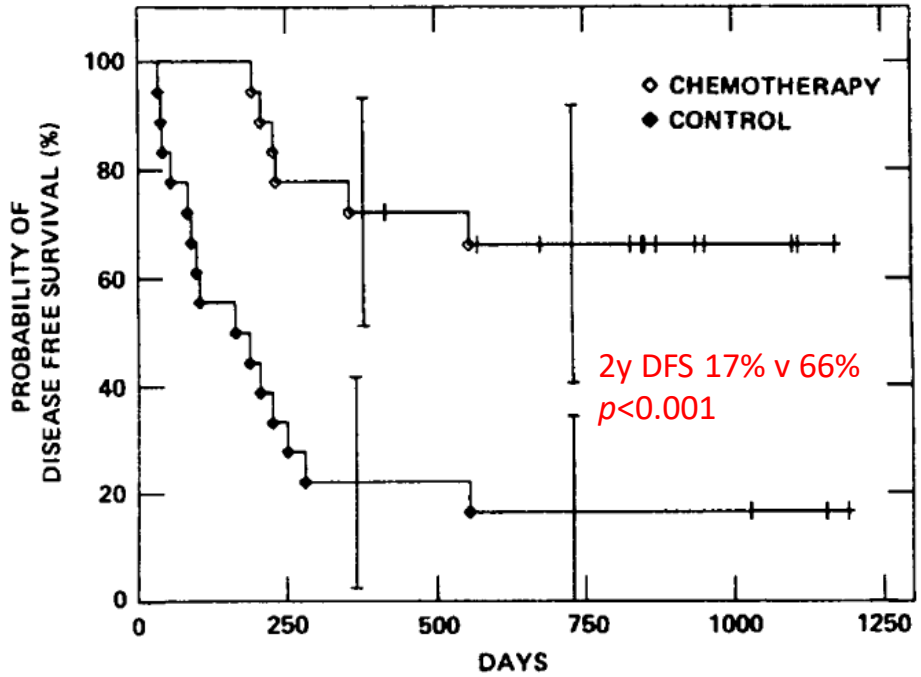
THE EFFECT OF ADJUVANT CHEMOTHERAPY ON RELAPSE-FREE SURVIVAL IN PATIENTS WITH OSTEOSARCOMA OF THE EXTREMITY

MICHAEL P. LINK, M.D., ALLEN M. GOORIN, M.D., ANGELA W. MISER, M.D., ALEXANDER A. GREEN, M.D., CHARLES B. PRATT, M.D., JEAN B. BELASCO, M.D., JON PRITCHARD, F.R.C.P., JAMES S. MALPAS, F.R.C.P., ALAN R. BAKER, M.D., JOHN A. KIRKPATRICK, M.D., ALBERTO G. AYALA, M.D., JONATHAN J. SHUSTER, PH.D., HERBERT T. ABELSON, M.D., JOSEPH V. SIMONE, M.D., AND TERESA J. VIETTI, M.D.



n=18 per arm

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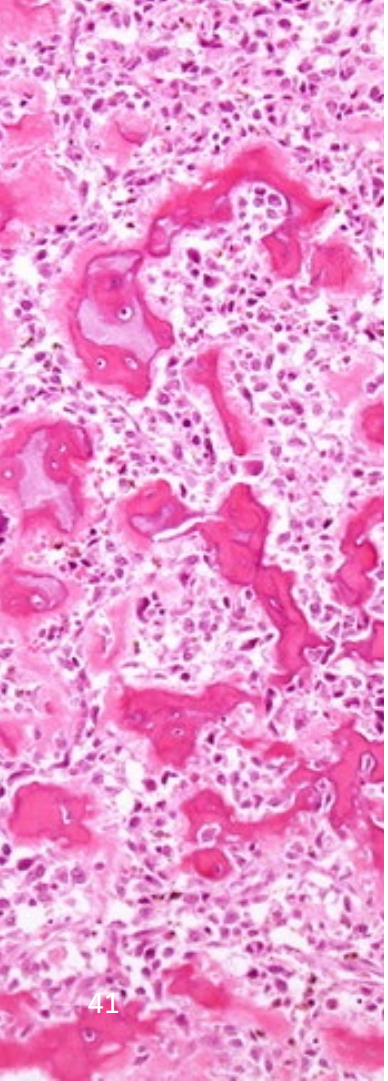

Localized osteosarcoma

- Glucarpidase After High-Dose Methotrexate in Adult Patients With Osteosarcoma (NCT03960177)

Advanced osteosarcoma

- SARC038: Phase 2 Study of Regorafenib and Nivolumab in Advanced Osteosarcoma (NCT04803877)

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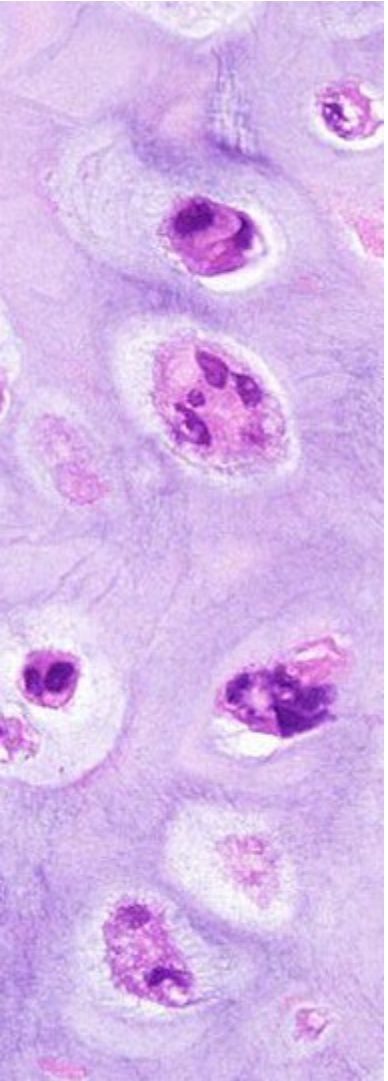

Chondrosarcoma

- Conventional chondrosarcoma is a surgical disease.
  - Limited efficacy of systemic therapies.
- *Open now*: INBRX-109 (a DR5 agonist) in Conventional Chondrosarcoma (NCT04950075, randomized, placebo-controlled phase 2)

Trial Available for Any Sarcoma Subtype (Bone or STS)

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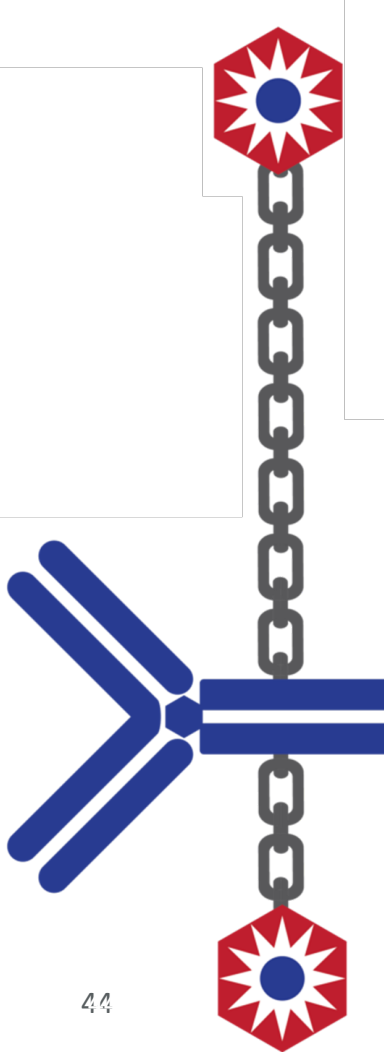

Advanced Sarcomas

- Mecobotamab vedotin (BA3011, CAB-AXL-ADC) ± Nivolumab Safety and Efficacy Study in Adult and Adolescent Patients With Sarcoma (NCT03425279, open-label Phase 2)
  - Molecular prescreening by AXL IHC

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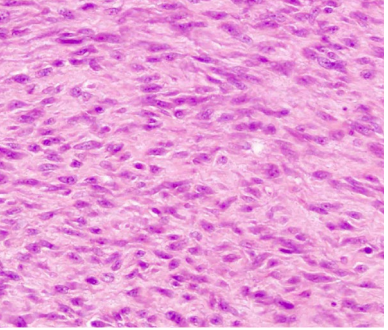
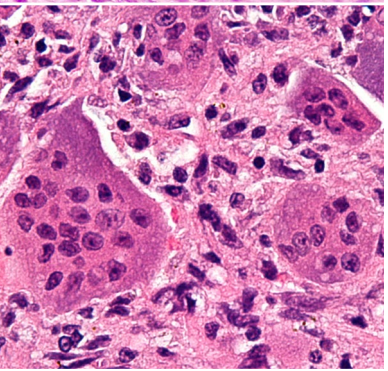
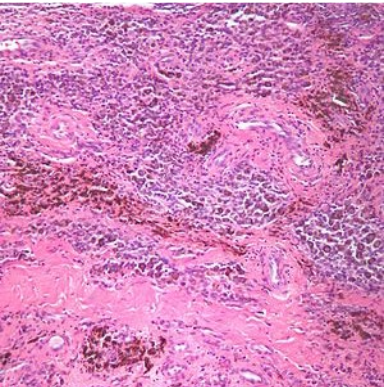
Benign, locally aggressive bone & soft tissue tumors







Benign, locally aggressive bone & soft tissue tumors

- Desmoid tumors
  - Avoid surgery. First line treatment is active surveillance. Second line treatment is medical therapy.
  - *Open now*: RINGSIDE: AL102 (oral gamma secretase inhibitor) in Patients With Progressing Desmoid Tumors (NCT04871282)
- Giant cell tumor of bone
  - Denosumab efficacious for unresectable disease.
- Tenosynovial giant cell tumor (TGCT)
  - Pexidartinib approved for diffuse, unresectable disease.
  - *Open now*: DCC-3014 (oral CSF1R inhibitor) in Patients With Advanced Tumors and Tenosynovial Giant Cell Tumor (NCT03069469)

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Conclusions

Key Take Aways

- Referral to an experienced sarcoma center is recommended.
  - Expert pathology review is essential.
  - First surgery is the best surgery; refer to sarcoma surgeon early.
- Prognosis for advanced STS is improving despite lack of “breakthrough” treatment.
- Numerous subtype-specific clinical trials may lead to additional approved treatment options.

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Extra slides (PRN)

Advanced STS

- Clinical trial
- Doxorubicin
- Ifosfamide
- Doxorubicin + ifosfamide
- Gemcitabine + docetaxel
- Dacarbazine (+/- gem)
- Pazopanib
- Trabectidin
- Eribulin

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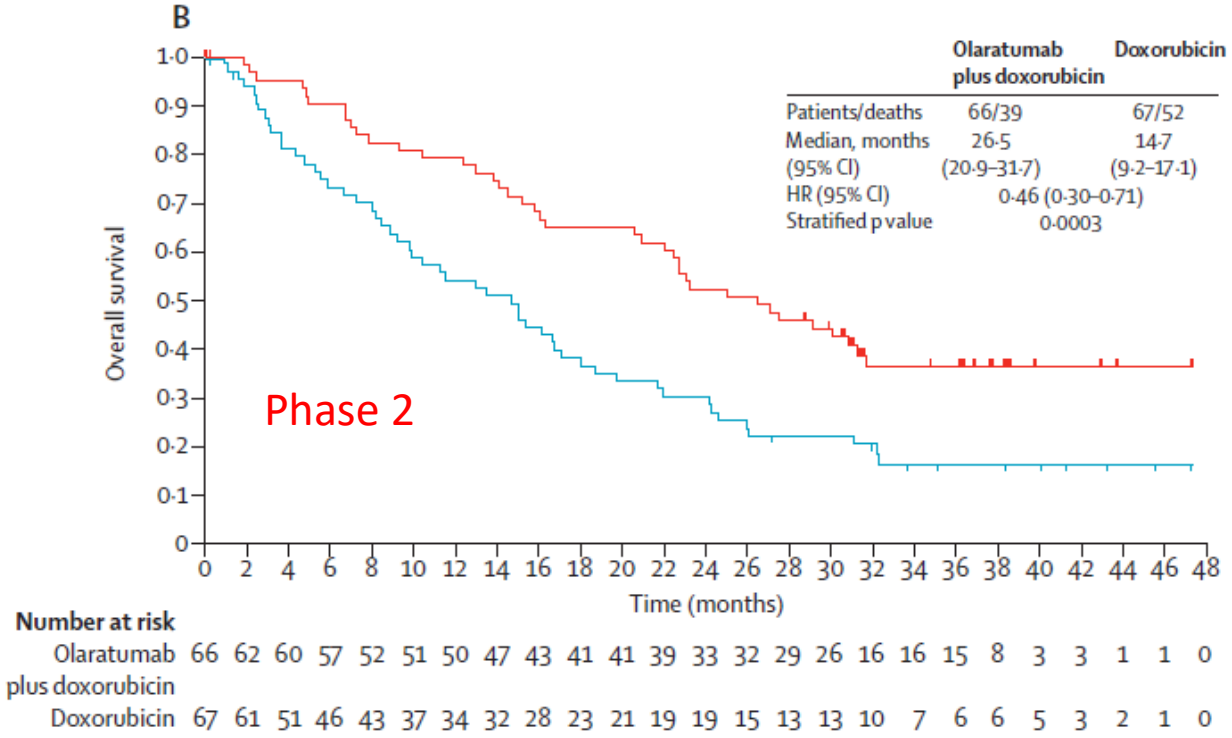
Olaratumab / Any Subtype STS



FDA approved Oct 2016

Tap 2016 Lancet

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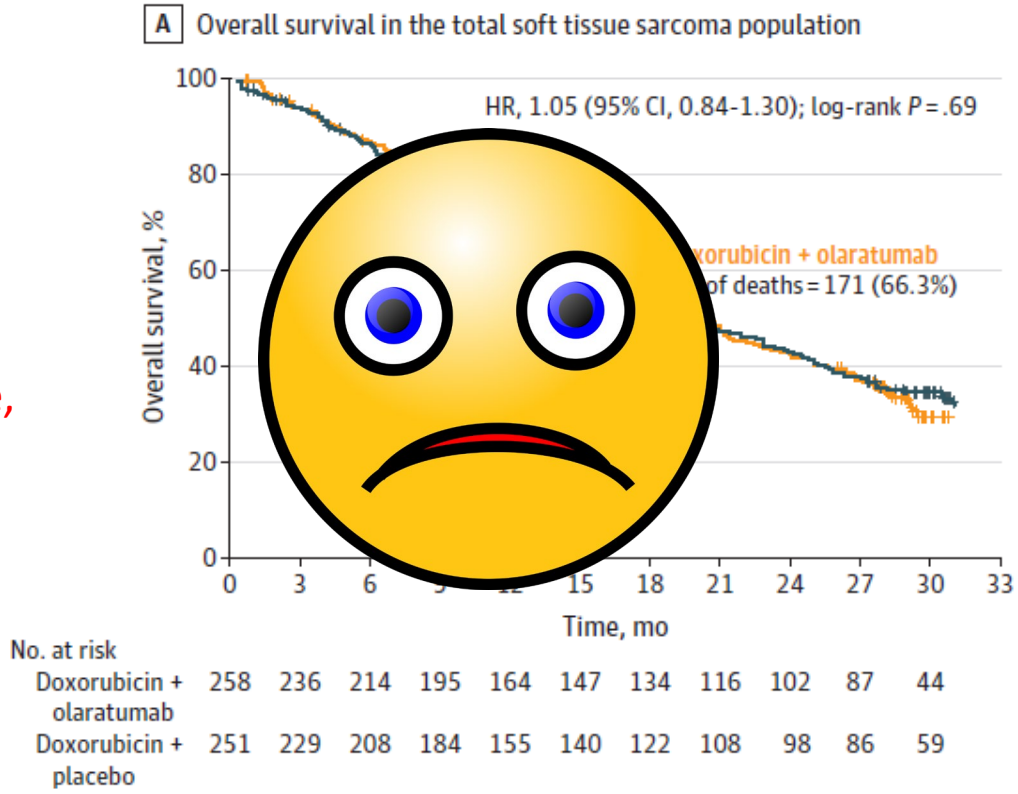
Olaratumab / Any Subtype STS

FDA advised against use, manufacture halted



Tap 2020 JAMA

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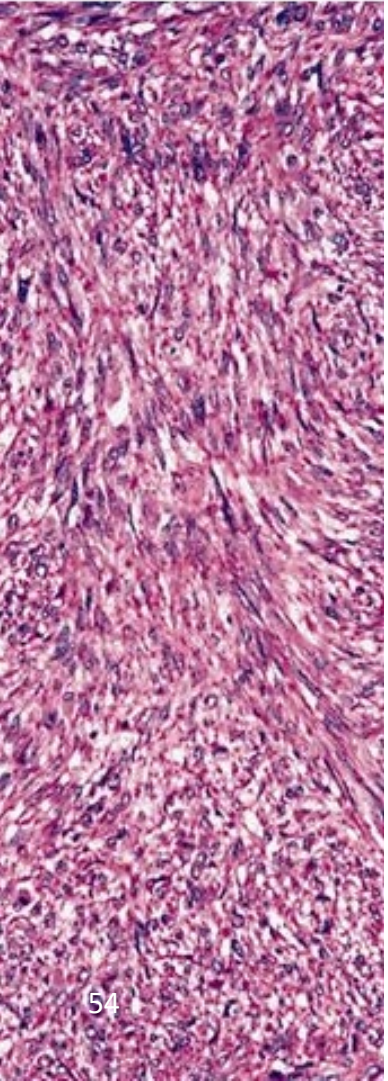
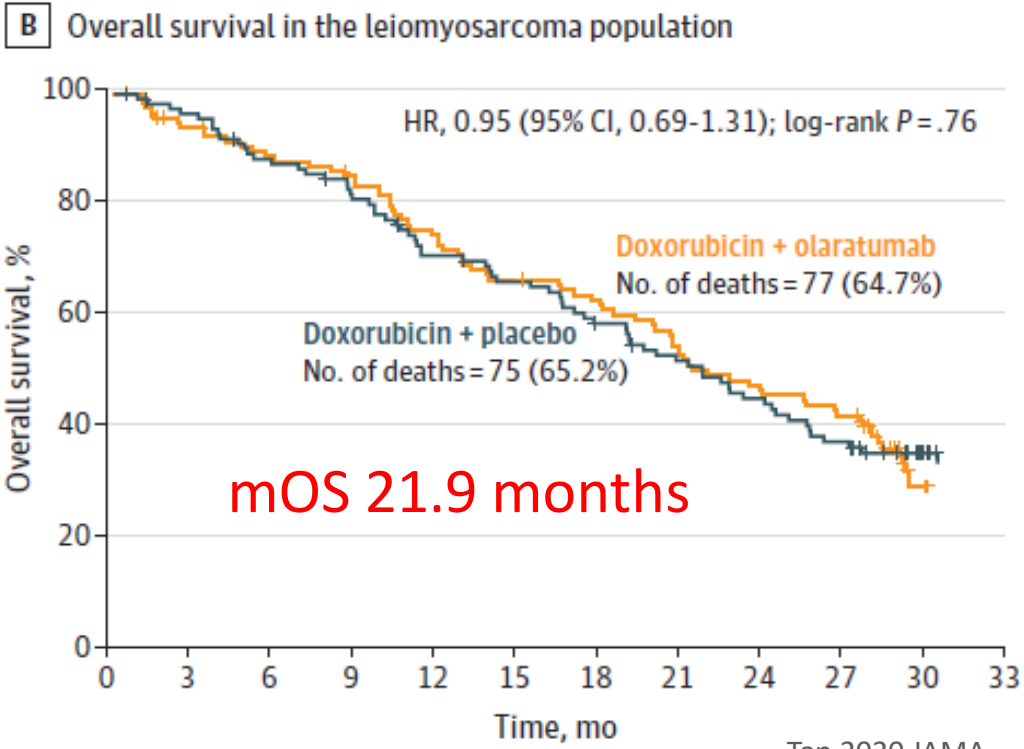


Advanced leiomyosarcoma



Tap 2020 JAMA

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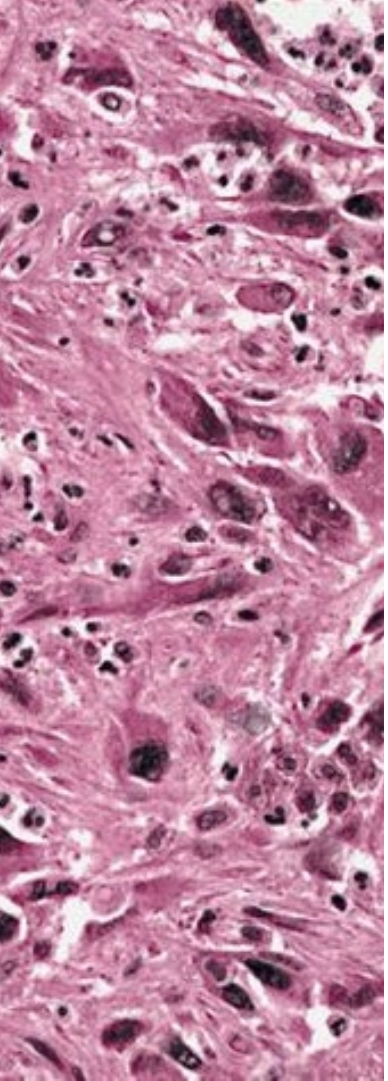
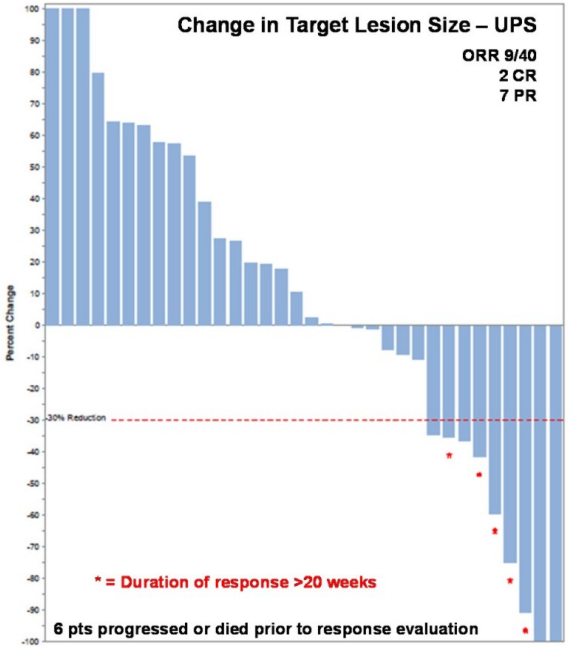


Checkpoint inhibition for STS

- SARC028 trial of pembrolizumab
  - ORR 18% in STS, including 4 of 10 with UPS
  - Expansion cohort for UPS:
    - ORR 23%
    - 25% of responders were PD-L1 neg
  - Limited activity in other subtypes



Tawbi et al, Lancet Oncol 2017 and Burgess ASCO 2019