Miami Cancer Meeting 2023

Soft-tissue Sarcomas

Diagnosis and Management

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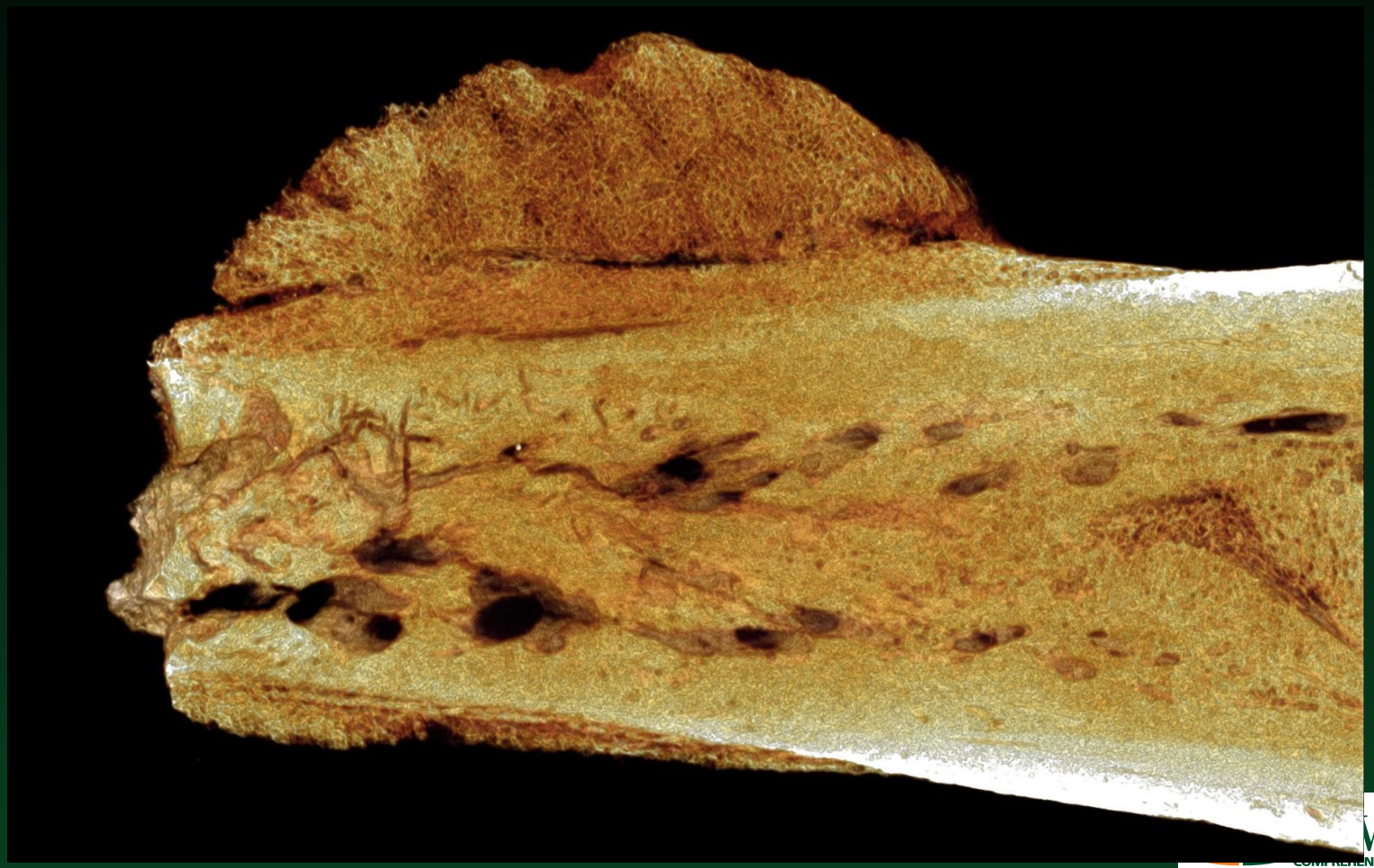
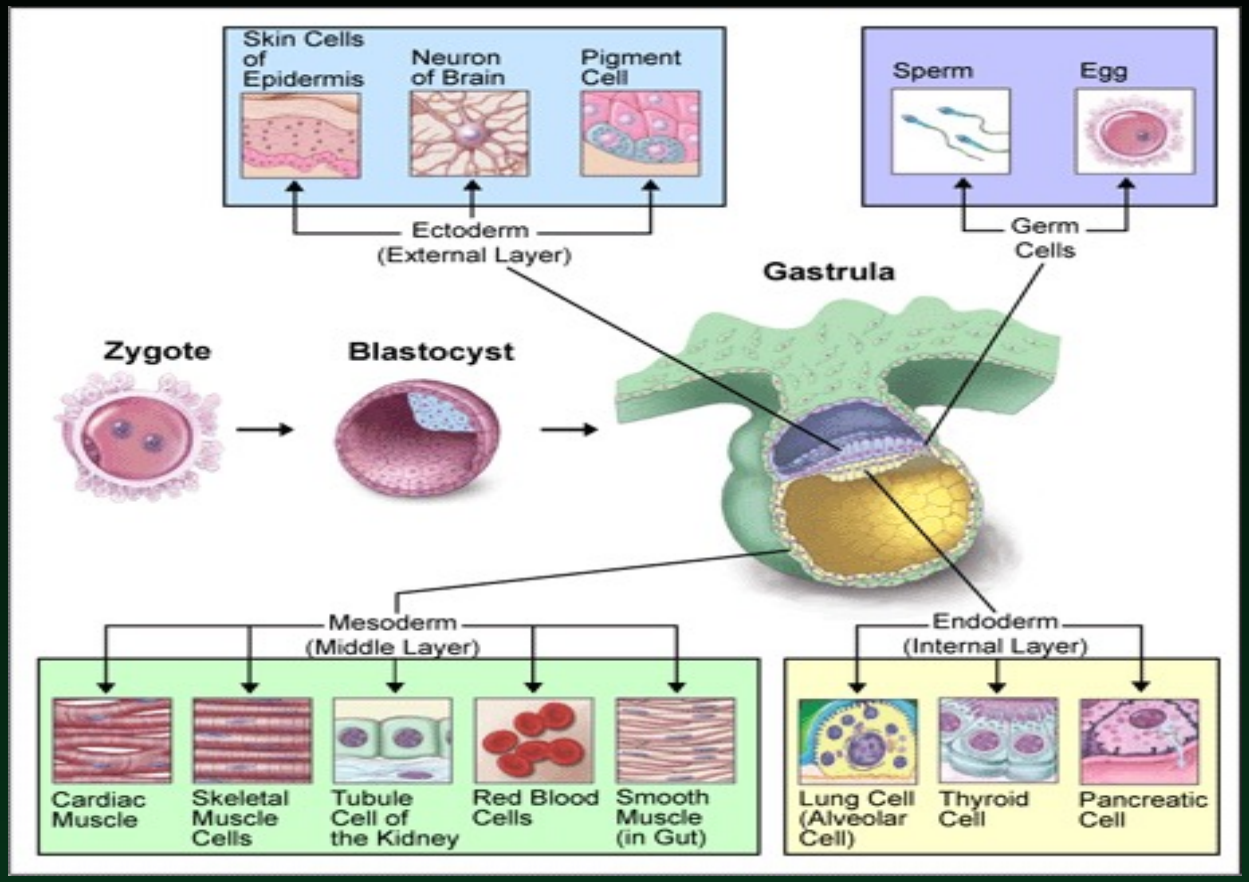
First Sarcoma (Osteosarcoma)

~1.7 million years ago



Randolph-Quinney, et al. SAJS, 2016



http://www.ncbi.nlm.nih.gov/About/primer/genetics_cell.html

Molecular Sarcomagenesis

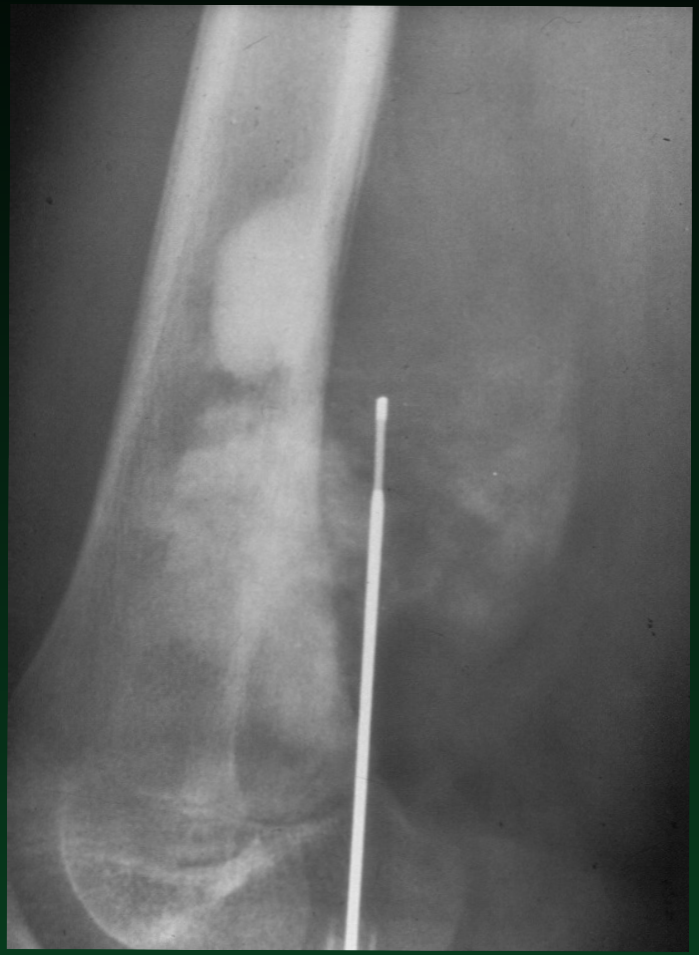
- **Point mutations**
  - GIST: *KIT, PDGFR, RAF*
  - Myxoid Liposarcoma: PTEN, PI3K, AKT
- **Gene Amplification**
  - Dediff Liposarcoma: MDM-2, CDK4
  - Neuroblastoma: *n-myc*
- **Gene Deletion**
  - Osteosarcoma: *p53*
  - Retinoblastoma*: RB1*
- **Translocation**
  - Ewing's Sarcoma: *EWS-FLI1*
  - Dermatofibrosarcoma*: Col1A-PDGFB*
- **Protein Overexpression**
  - Desmoid Tumor: ER

Anatomic Distribution

Location	Percentage
Head and neck	10
Thorax	10
Abdomen	11
Pelvis	8
Upper Extremity	16
Lower Extremity	29
Unknown	17

Diagnosis

Tru-Cut (Core) Biopsy



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Discrepancies Between Primary Diagnosis and Second Opinion in Patients With Sarcoma

Study	Full Agreement With Second Opinion, %	Minor Discrepancy With Partial Discordance, %	Major Discrepancy With Complete Discordance, %
Lurkin et al[1] N = 366	54	27	19
Arbiser et al[2] N = 266	68	7	25

1. Lurkin et al. *BMC Cancer* 2010;10:150.
2. Arbiser et al. *Am J Clin Pathol.* 2001;116:473-476.

Management

Metastatic Soft-tissue Sarcoma

Current Classification of Sarcomas

- **Vascular STSs**
  - Angiosarcoma
  - Hemangiosarcoma
  - Lymphangiosarcoma
  - Hemangioendothelioma
  - Hemangiopericytoma
  - Kaposi's Sarcoma
- **Neural STSs**
  - Malignant Peripheral Nerve Sheath Tumor
  - Malignant Paraganglioma
  - Neuroblastoma, Neuroepithelioma
  - Granular Cell Tumor
- **Adipose STSs**
  - ALT
  - Myxoid/Round cell Liposarcoma
  - Dedifferentiated Liposarcoma
- **Pleomorphic STSs**
  - Lipo, MFH
- **Neuromuscular STS**
  - GI Stromal Tumor
- **Unclassified**

N=175

- **Smooth Muscle STSs**
  - GI, GU, Cutaneous, Vascular
- **Skeletal Muscle STSs**
  - ARMS, ERMS, Pleomorphic RMS
- **Fibrous STSs**
  - Fibrosarcoma
  - Fibromyxoid Sarcomas
  - Desmoid Tumor
  - Dermatofibrosarcoma
  - Inflammatory myofibroblastic tumor
- **Unknown Tissue**
  - Synovial Sarcoma
  - ASPS
  - Epithelioid Sarcoma
- **Bone Sarcomas**
  - Osteosarcoma (+ variants)
  - Chondrosarcoma (+ variants)
  - Giant Cell Tumor of Bone
  - Ewing's Sarcoma Family of Tumors
- **Extraskeletal Bone Sarcomas**
  - Osteosarcoma
  - Ewing's Sarcoma C

Soft Tissue Sarcomas

Sites of Metastases

- **Lung: most; but rare with GIST, desmoid tumor, DFSP**
- **Liver: GIST, Leiomyosarcoma, Angiosarcoma**
- **Fat: Myxoid liposarcoma**
- **Brain: Angiosarcoma, ASPS**
- **Bone: PNET, Angiosarcoma, Hemangioendothelioma**
- **Lymph Nodes: Epithelioid Sarcoma, SDH-deficient GIST, Clear cell sarcoma, Angiosarcoma**

Soft-tissue Sarcomas

Active Systemic Agents

- Adriamycin
- Ifosfamide
- High-dose ifosfamide
- DTIC, Temozolomide
- Gemcitabine
- Docetaxel, Paclitaxel
- Irinotecan
- Vincristine
- VP-16
- Trabectedin
- Imatinib, sunitinib, regorafenib, ripretinib, avapritinib
- Pazopanib
- Eribulin
- Tazemetostat
- Denosumab
- mTOR inhibitors
- Niragacestat

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Soft-tissue Sarcomas

Sensitivity to Systemic Agents

- **Very sensitive histologies :**
  - Ewing's/PNET, Rhabdomyosarcoma, DSRCT, GIST, DFSP, Angiosarcoma, Myxoid/round cell sarcoma
  - Desmoid Tumors, Solitary Fibrous Tumor
- **Intermediately sensitive histologies :**
  - fibrosarcoma, MPNST, solitary fibrous tumor, Extraskeletal myxoid chondrosarcoma, synovial, leiomyosarcoma, Alveolar Soft-parts Sarcoma, PEComa
- **Minimally sensitive histologies:**
  - Epithelioid sarcoma, dediff liposarcoma,
- **Resistant histologies:**
  - Clear-cell sarcoma, GI leiomyosarcoma, Epithelioid Hemangioendothelioma

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Doxorubicin Plus Ifosfamide (AI) Prospective Trials for STS

Dose	No. of Pts.	RR%
AI (50/5000 mg/m^2)	258	25
AI (60/7500 mg/m^2)	88	34
AI (75/5000 mg/m^2)	104	45
AI (75-90/10,000 mg/m^2)	79	65

Santoro *et al. JCO*. 13:1537-1545, 1995.

Edmonson *et al. JCO.* 11:1269, 1993

Steward *et al. JCO.* 11:15-21, 1993.

Patel et al, 2000

Doxorubicin + Ifosfamide is Superior to Doxorubicin Alone

(intention to treat analysis)

OS

PFS

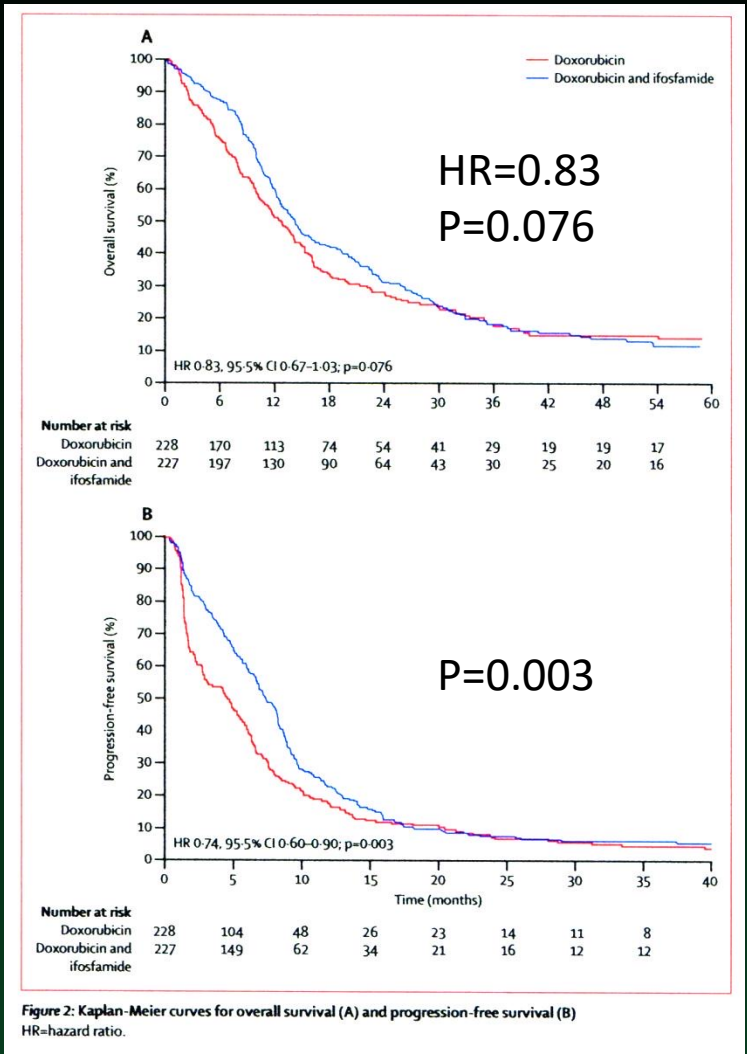

Figure 2: Kaplan-Meier curves for overall survival (A) and progression-free survival (B)
HR=hazard ratio.

Overall response rate:
Doxorubicin: **13.6%**
Doxorubicin + ifosfamide: **26.5%**

Median PFS
Doxorubicin: **4.6 mths**
Doxorubicin + ifosfamide: **7.4 mths**

Median overall survival:
Doxorubicin: 12.8 mths
Doxorubicin + ifosfamide: 14.3 mths
1.5 month increase in median OS

1 Year Overall Survival
Doxorubicin: **51%**
Doxorubicin + ifosfamide: **60%**

Judson et al Lancet Oncol 2014;15(14):415-23

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RECIST "Best response" data
(n=116 evaluable)

	Gem (n=47)	Gem / Doc (n=69)	TOTAL
PR/CR	4 (9%)	13 (19%)	17 (15%)
SD	24 (51%)	37 (54%)	61 (53%)
SD: 24 week	9 (19%)	12 (17%)	21 (18%)
PD	19 (40%)	19 (27%)	38 (32%)

Soft Tissue Sarcomas

Temozolomide Chemotherapy

- Two-arm phase 2 study, GISTs vs. others
- 85 mg/m^2 PO daily
- 0/17 responses in GISTs
- **4/39 PRs (9%)** in other histologies
  - **2/13 (15%) leiomyosarcomas** (uterus, RP, vascular)
- Well tolerated

Trent et al. Cancer 19:3483-

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Pazopanib vs Placebo in PALETTE

Efficacy

- **Progression-Free Survival**
  - Pazopanib= 4.6 months
  - Placebo= 1.6 months
  - HR = 0.31
  - 95% CI 0.24–0.40; *P*<0.001)
- **Overall Survival**
  - Pazopanib= 12.5 months
  - Placebo= 10.7 months
  - HR = 0.86
  - 95% CI 0.67–1.11; *P*=0.2514)

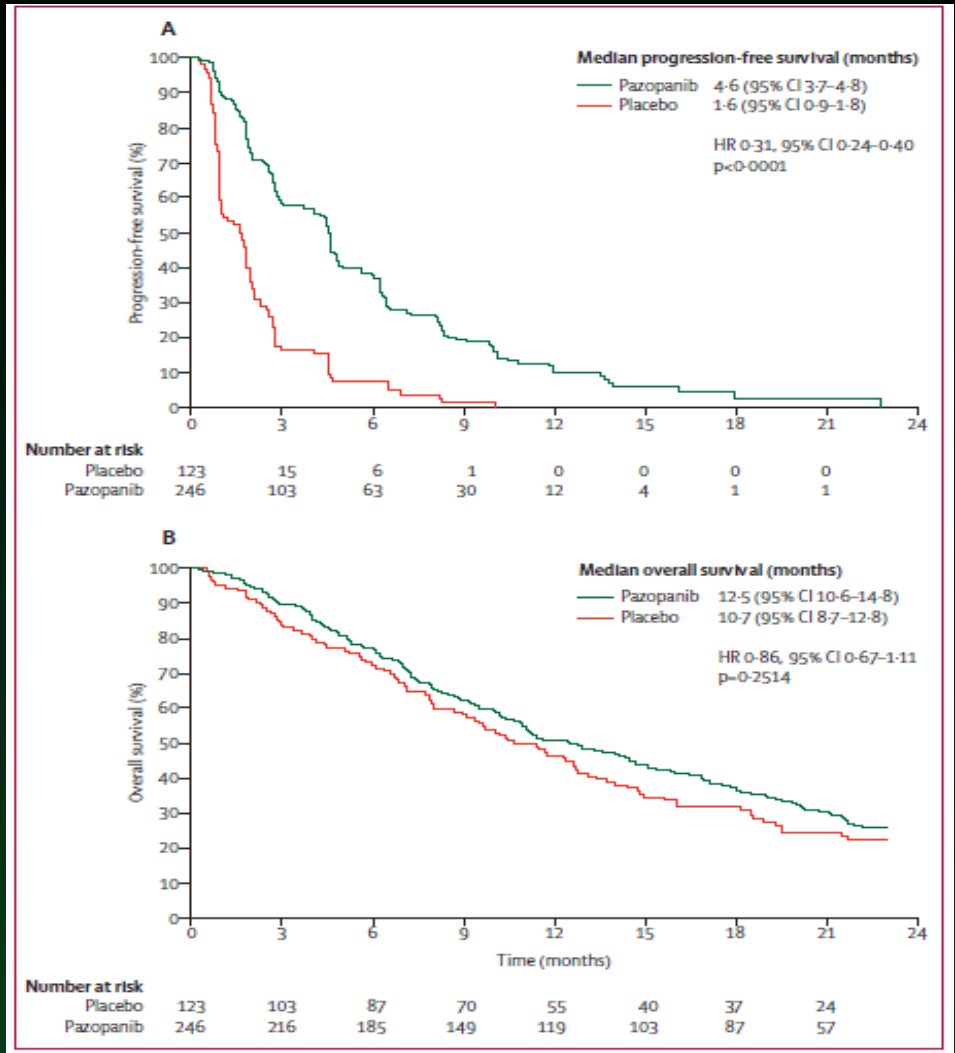
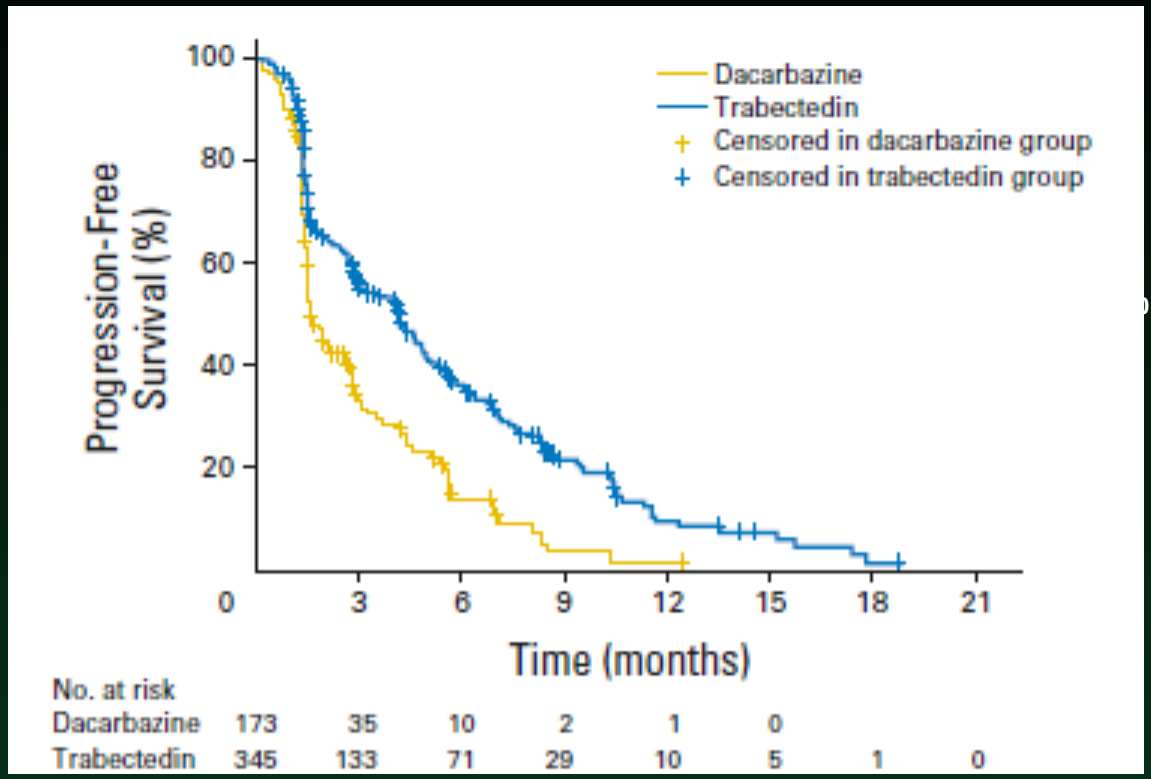


Figure 2: **Kaplan-Meier curves for survival**
Progression-free (A) and overall (B) survival. 106 patients died or had disease progression in the placebo group, 168 in the pazopanib group (cutoff Nov 22, 2010). 95 patients died in the placebo group, 185 in the pazopanib group (cutoff Oct 24, 2011).

HR = hazard ratio; CI = confidence interval.

van der Graff WT et al. *Lancet*. 2012;379:1879-1886.

Trabectedin vs Dacarbazine: PFS
Liposarcoma and Leiomyosarcoma



- PFRs at 3 and 6 months
  - Trabectedin= 56% and 37%
  - Dacarbazine= 34% and 14%

Demetri GD et al. *J Clin Oncol.* 2016;34:786-793.

Precision Oncology

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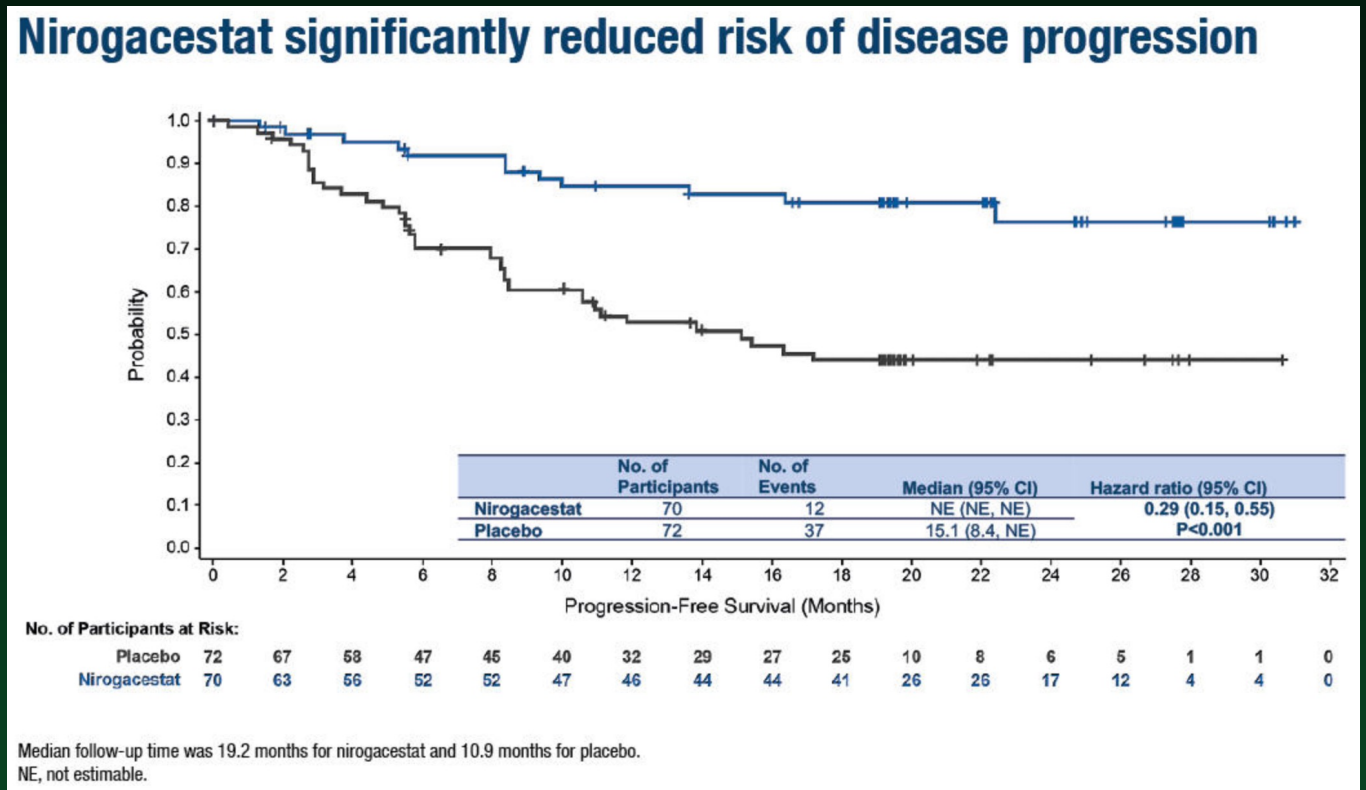
Phase 3 Niragacestat vs Placebo
Desmoid Tumor

- 142 adults with progressing desmoid tumours
- Oral gamma secretase inhibitor (GSI)
- 71% reduction in the risk of progression vs placebo
  - hazard ratio for progression-free survival 0.29, p<0.001
- Significantly increased the objective response rate
  - 41% versus 8%, p<0.001
- More rapid median time to response
  - 5.6 months versus 11.1 months

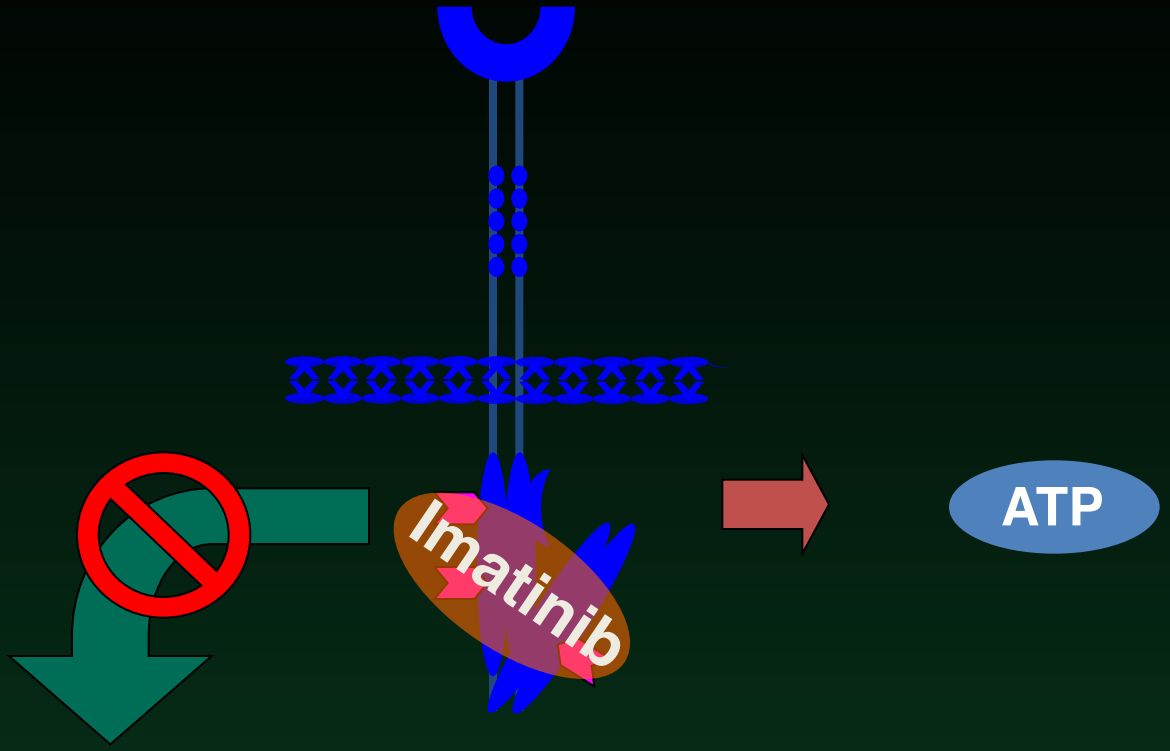


ESMO 2022

GIST Overview

- Most common GI sarcoma
  - 0.2% of all GI tumors, but 80% of GI sarcomas
- High frequency of metastatic disease
- Gene mutations drive phenotype and therapy
- Metastatic disease treated with tyrosine kinase inhibitors (TKIs)
  - **Imatinib** (PFS = 24 months)
  - **Sunitinib** (PFS = 6 months)
  - **Regorafenib** (PFS = 5 months)
  - **Ripretinib** (PFS = 6.3 months)
  - **Avapritinib (PFS = 3.7 months)**
  - **Avapritinib PDGFR (PFS = NR)**

Kit Receptor Phenotype



Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

= imanitib contact

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GIST Subtypes and Treatment

- Kit exon 11: Imatinib 400 mg
- Kit exon 9: Imatinib 800mg (or tolerated dose)
- PDGFR D842V: avapritinib
- SDH deficiency: Sunitinib or Regorafenib (TMZ trial)
- Raf V600E: Raf inhibitor
- NF-1, Ras: Raf or Mek inhibitor
- PI3K: mTOR inhibitor
- IGF-1R expressing – IGF-1R inhibitor trial
- TRK fusion – Larotrectenib NTRK inhibitor
- KIT resistance mutations
  - Exon 13 (ATP binding site): Sunitinib 37.5 mg daily
  - Exon 17 (A-loop): Regorafenib or Ripretinib

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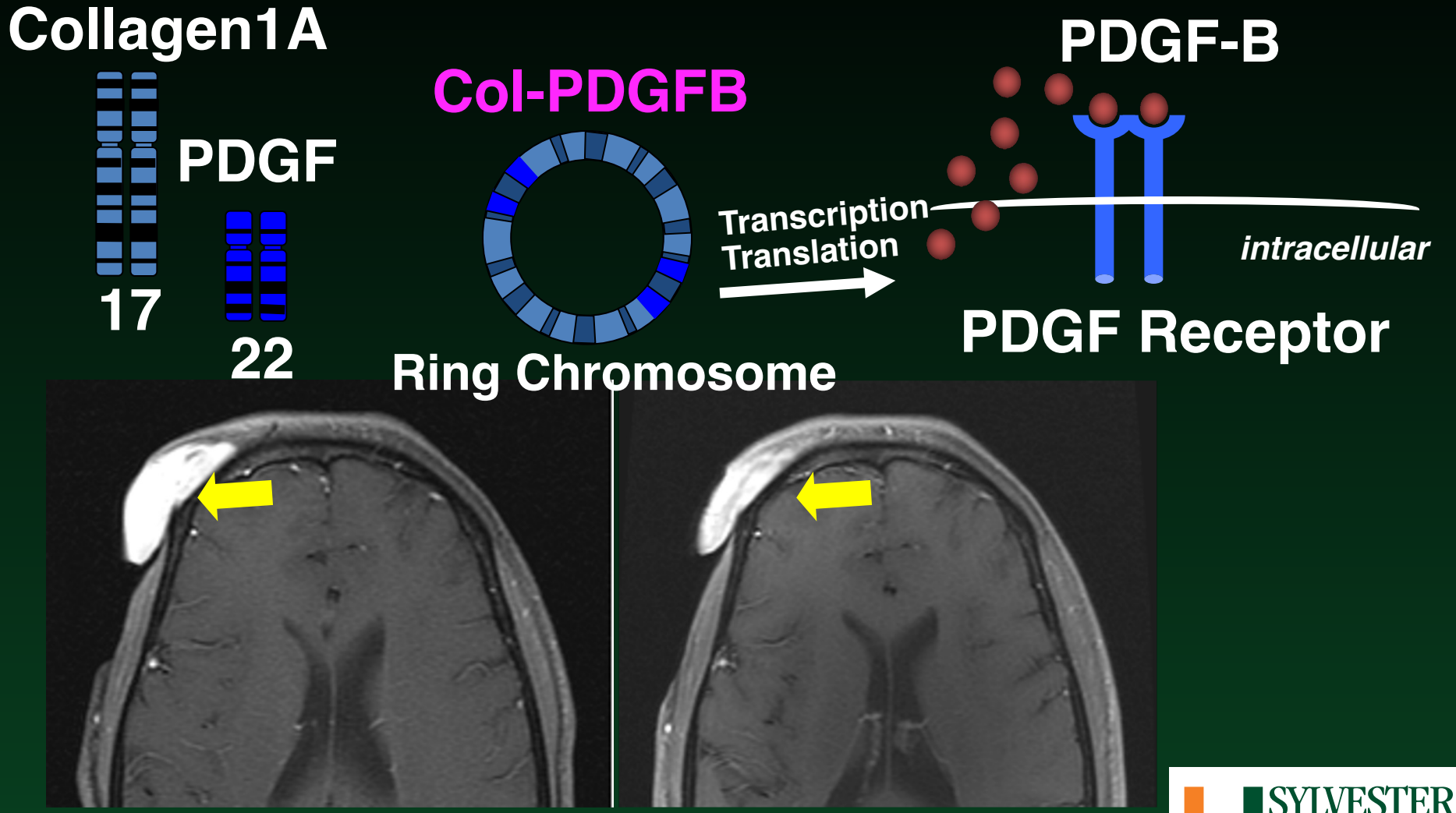
PDGFR Inhibitors in Dermatofibrosarcoma



Tibes, Trent, Kurzrock. Ann Rev Pharmacol Toxicol. 45:357-84

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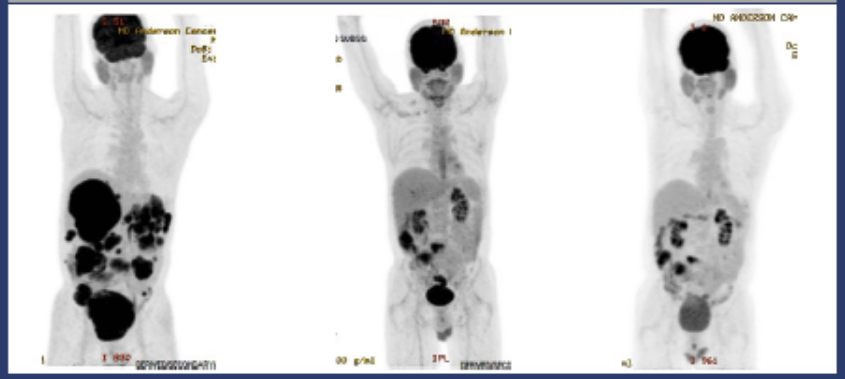
Sarcoma With TRK Fusion

Patient #2:
ETV6-NTRK3 fusion

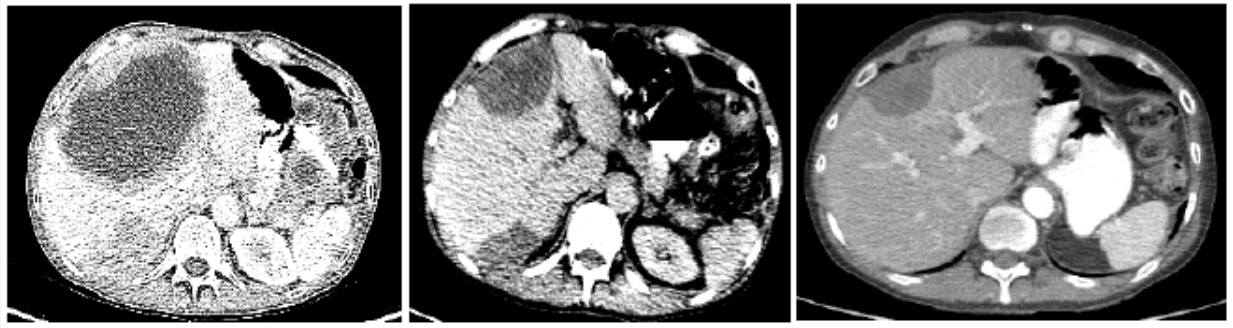
Larotrectinib
Entrectinib

PET



Study baseline | Study cycle 3 day 1 | Study cycle 9 day 1

CT



Study baseline | Study cycle 5 day 1 | Study cycle 9 day 1

Conclusions

- “Sarcoma” is a collection of 175 unique types of primary bone or soft-tissue cancers
- Diagnosis by an experienced Sarcoma pathologists is recommended
- Dose intense, cytoxic chemotherapy is standard front-line therapy for treatment of primary and most metastatic sarcoma types
- Precision medicine approaches are critical in select sarcoma types

Sarcoma Team

- **Medical Oncology**
  - Jon Trent
  - Gina D'Amato
  - Emily Jonczak
  - Steve Bialick
  - Aditi Dhir (Ped)
- **Pathology**
  - Andrew Rosenberg
  - Elizabeth Montgomery
  - Daniel Cassidy
  - Jay-Lou Velez Torres
- **Radiology**
  - Ty Subhawong
  - Francesco Alessandrino
- **Nurse Practitioner**
  - Morgan Smith
  - Solange Sierra
  - Ali Naveda
- **Nursing**
  - Arlen Pita
  - Rosario Jara
  - Francess Donna
- **Social Work**
  - Marlene Morales
  - Adriana Alvaraez (AYA)

- **Orthopedic Oncology**
  - Fran Hornicek
  - Tom Temple
  - Sheila Conway
  - Brooke Crawford
  - Mo Al Maaieh
- **Surgical Oncology**
  - Nipun Merchant
  - Alan Livingstone
  - Julie Grossman
- **Radiation Therapy**
  - Raphael Yechieli
  - Aaron Wolfson
  - Laura Freedman
- **Head & Neck Surgery**
  - Don Weed
  - Zoukaa Sargi
  - Frank Civantos
- **Thoracic Surgery**
  - Dao Nguyen
  - Nestor Villamizar

- **Interventional Radiology**
  - **Shree Venkat**
  - **Felipe de Souza**
- **Gynecologic Oncology**
  - **Matt Schlumbrecht**
  - **Abed Sinno**
- **Clinical Research**
  - **Josefina Sanchez**
  - **Julie de Leon**
  - **Adriana Martinez**
- **Lab Research**
  - **Zhefeng Duan, PhD**
  - **Luyuan Li, PhD**
  - **Karina Galoian**
  - **Josie Eid, PhD**
- **Fellows/Residents**
  - **Leti Campoverde**
  - **Priscella Coelho**
  - **Steven Bialick**
  - **Brandon Rose**

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