

Bone and Soft-tissue Sarcomas

19th Annual New Orleans Summer Cancer Meeting

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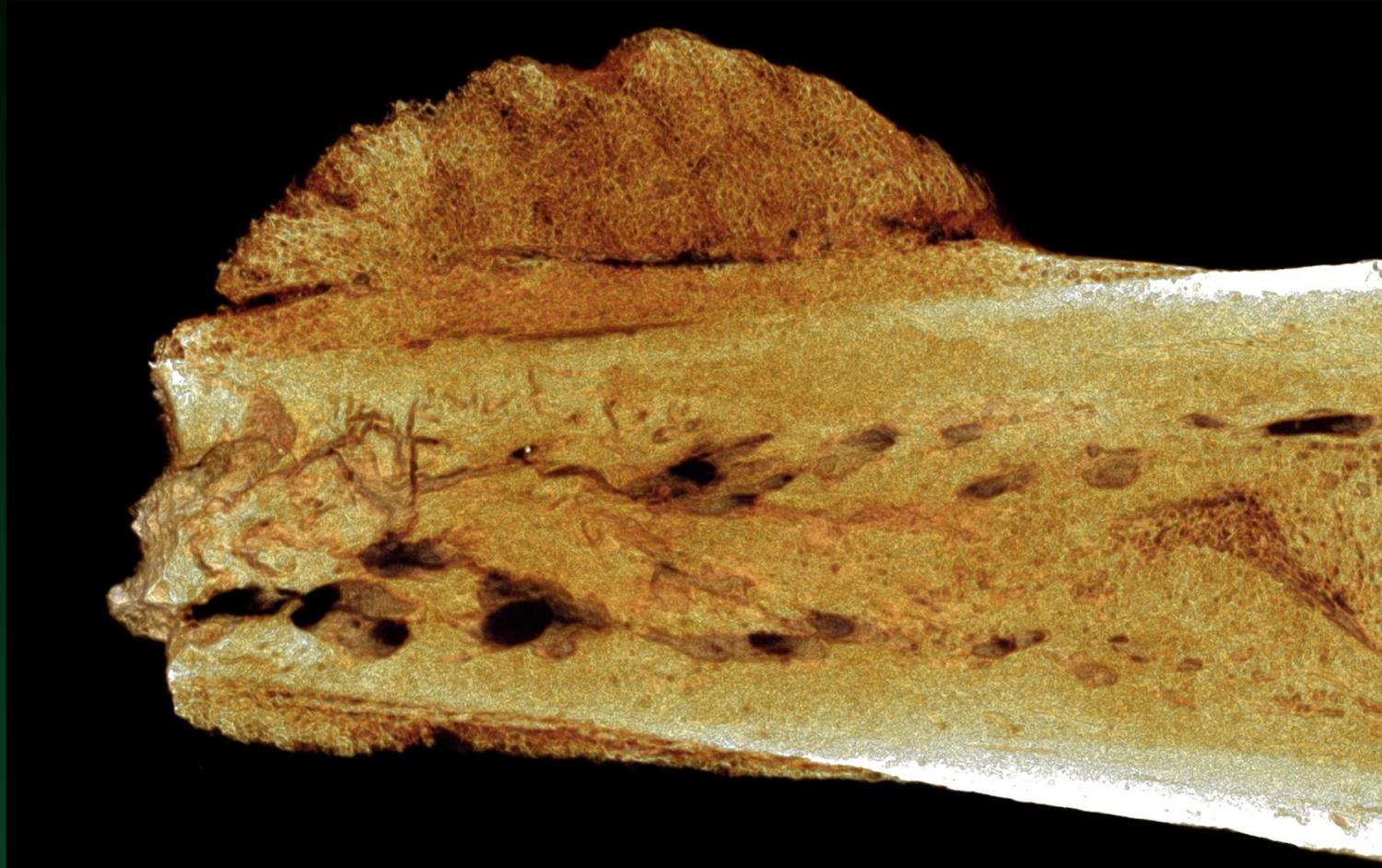
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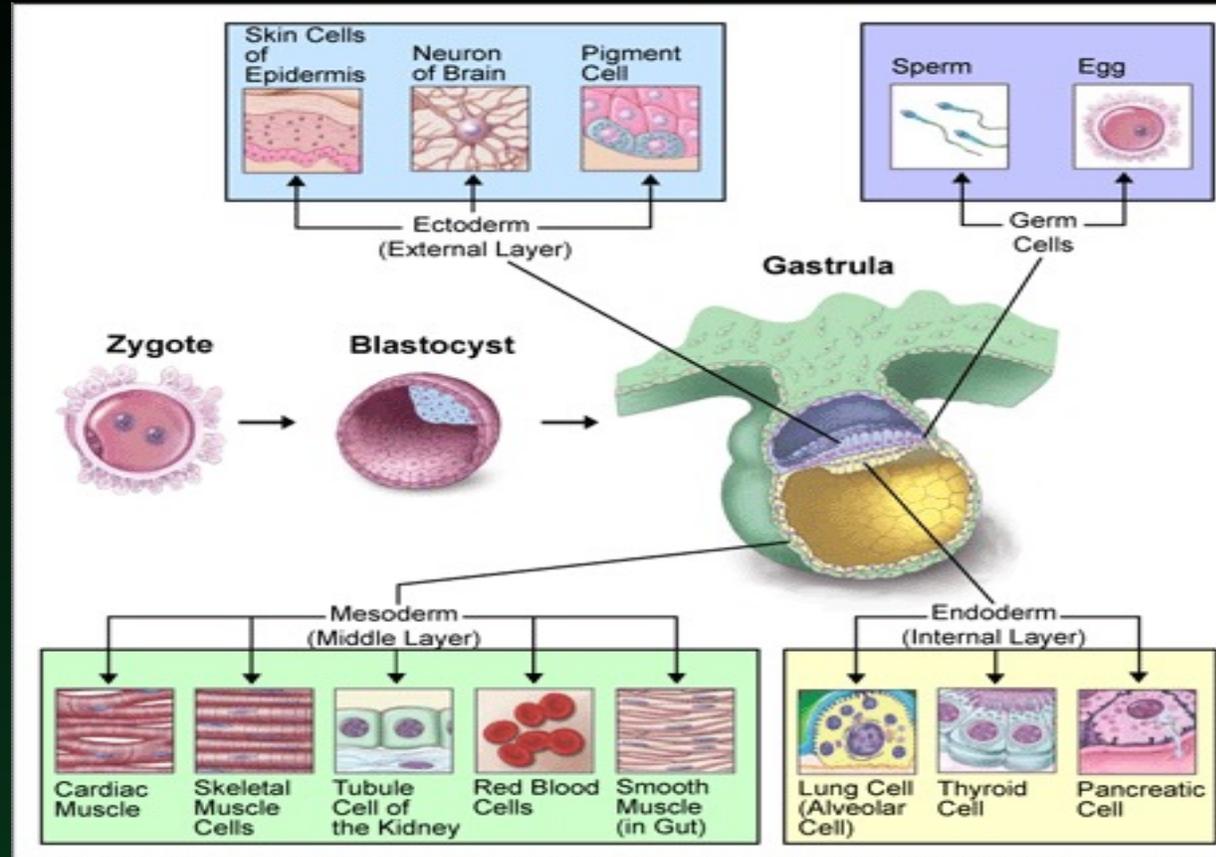
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First Sarcoma (Osteosarcoma)

~1.7 million years ago



Randolph-Quinney, et al. SAJS, 2016



Molecular Sarcomagenesis

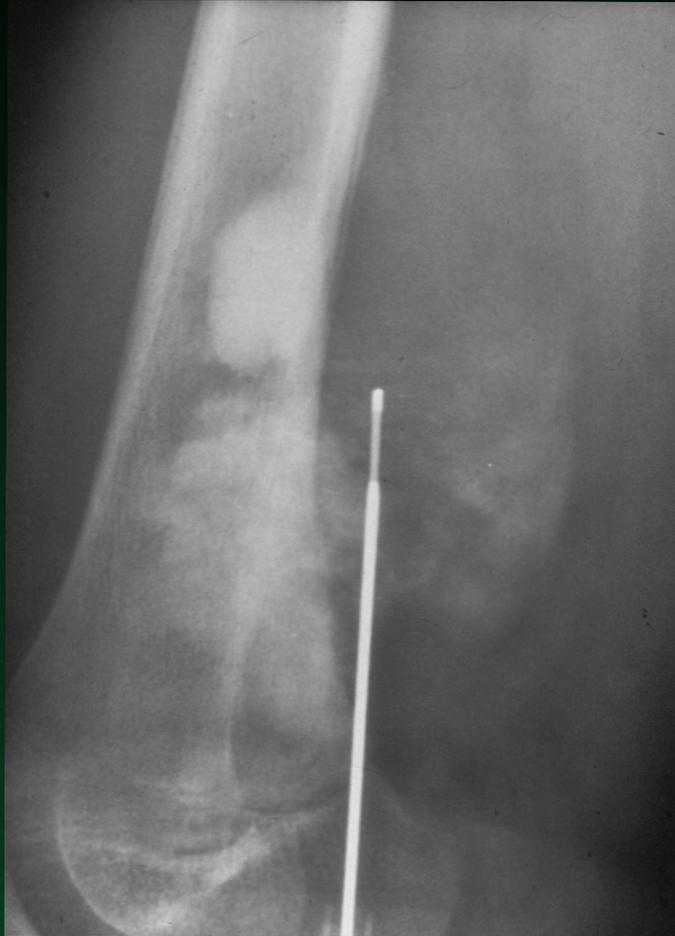
- **Point mutations**
 - GIST: *KIT, PDGFR, RAF*
 - Myxoid Liposarcoma: *PTEN, PI3K, AKT*
- **Gene Amplification**
 - Dediff Liposarcoma: *MDM-2, CDK4*
 - Neuroblastoma: *n-myc*
- **Gene Deletion**
 - Osteosarcoma: *p53*
 - Retinoblastoma: *RB1*
- **Translocation**
 - Ewing' s Sarcoma: *EWS-FLI1*
 -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



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.

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**
- **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
- **Extraskkeletal Bone Sarcomas**
 - Osteosarcoma
 - Ewing' s Sarcoma Chondrosarcoma

N=175

Soft Tissue and Bone 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

Management

Metastatic Soft-tissue Sarcoma

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
- Nirogacestat

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, Extraskkeletal 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

Advanced Soft-tissue Sarcomas

Single Agent Doxorubicin Efficacy

Doxorubicin Dose	Objective Response Rate
45 mg/m ²	18 %
60 mg/m ²	20 %
75 mg/m ²	37 %
Various	5-25%

O'Bryan et al, *Cancer* 1977
Judson et al, *Lancet Onc* 2014

Single Agent Ifosfamide Efficacy

Ifosfamide Dose (Gm/m²)	Objective Response Rate
6	10 %
8	17 %
10	21 %
14 (infusion)	29 %
14 (bolus)	57 %

Patel JCO 1997

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.

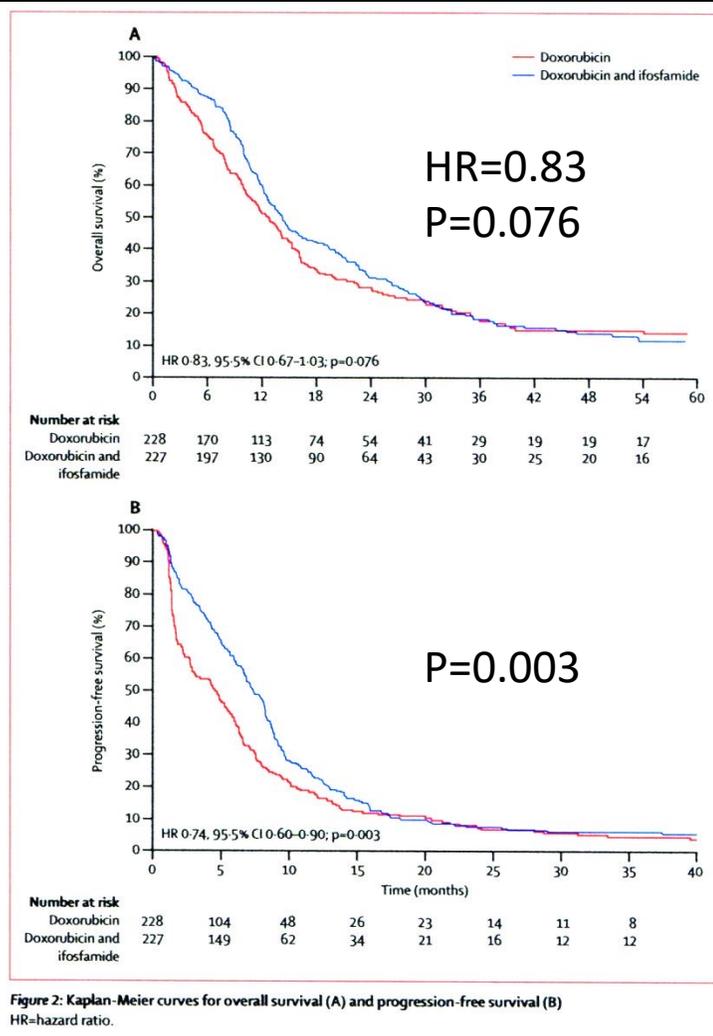
Edmonson *et al.* *JCO.* 11:1269, 1993

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

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%**

RECIST “Best response” data (n=116 evaluable)

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

Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial

Lancet Oncol 2017;
18: 1397-410

Beatrice Seddon, Sandra J Strauss, Jeremy Whelan, Michael Leahy, Penella J Woll, Fiona Cowie, Christian Rothermundt, Zoe Wood, Charlotte Benson, Nasim Ali, Maria Marples, Gareth J Veal, David Jamieson, Katja Küver, Roberto Tirabosco, Sharon Forsyth, Stephen Nash, Hakim-Moulay Dehbi, Sandy Bear

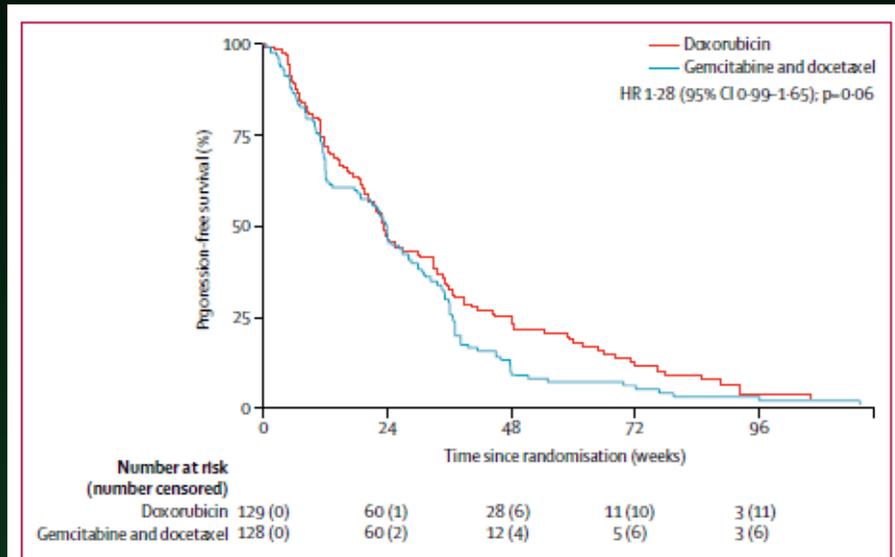


Figure 2: Progression-free survival
HR=hazard ratio.

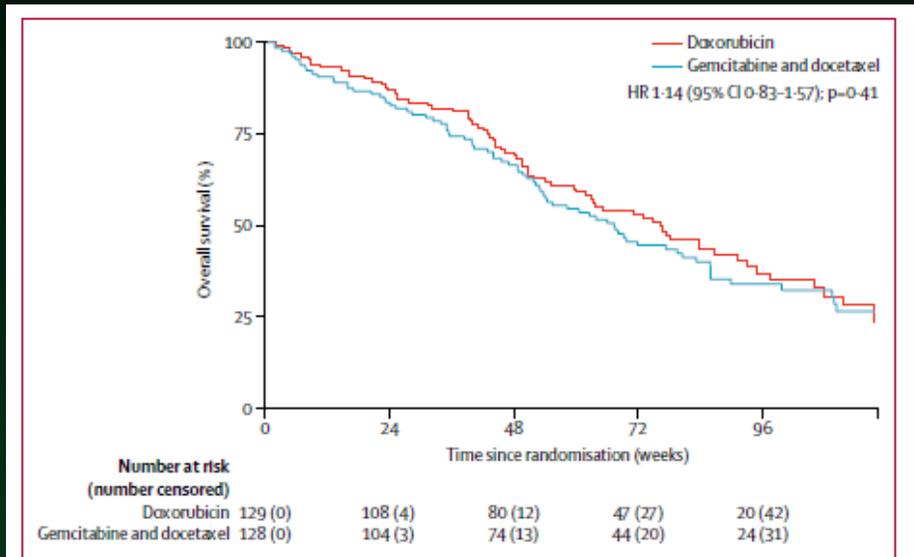
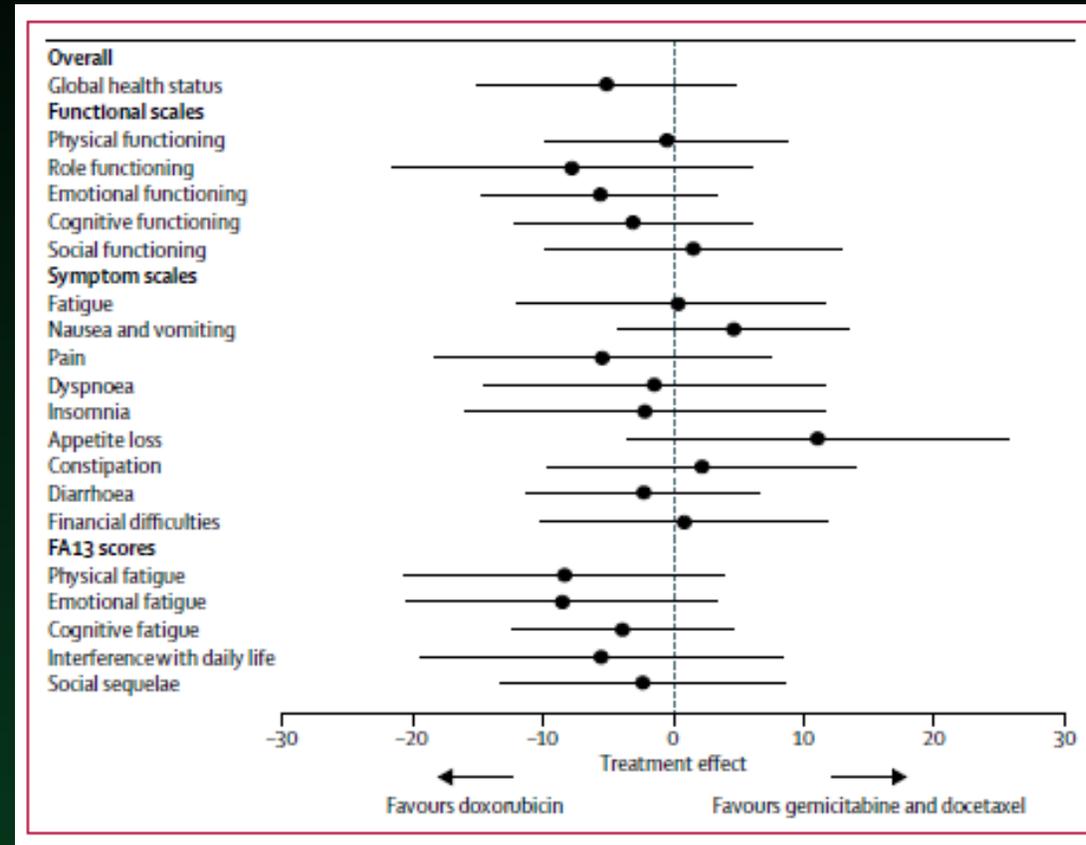


Figure 3: Overall survival
HR=hazard ratio.

Toxicity

doxorubicin vs Gem/doce

- The combination (G+D) should not be considered as routine, while doxorubicin should remain standard of care, in the first line setting for Soft Tissue Sarcoma (regardless of subtype)



Soft Tissue Sarcomas

Temozolomide Chemotherapy

- Two-arm phase 2 study, GISTs vs. others
- 85 mg/m² PO daily
- 0/17 responses in GISTs
- **4/39 PRs (9%)** in other histologies
 - **2/13 (15%) leiomyosarcomas** (uterus, RP, vascular)
- Well tolerated

Pazopanib vs Placebo in PALETTE Efficacy

- Pazopanib was associated with significantly longer **PFS (4.6 months vs 1.6 months; HR = 0.31, 95% CI 0.24–0.40; $P < 0.001$)** (figure A).
- Differences in OS between pazopanib and placebo were not significant (12.5 months vs 10.7 months; HR = 0.86, 95% CI 0.67–1.11; $P = 0.2514$) (figure B).

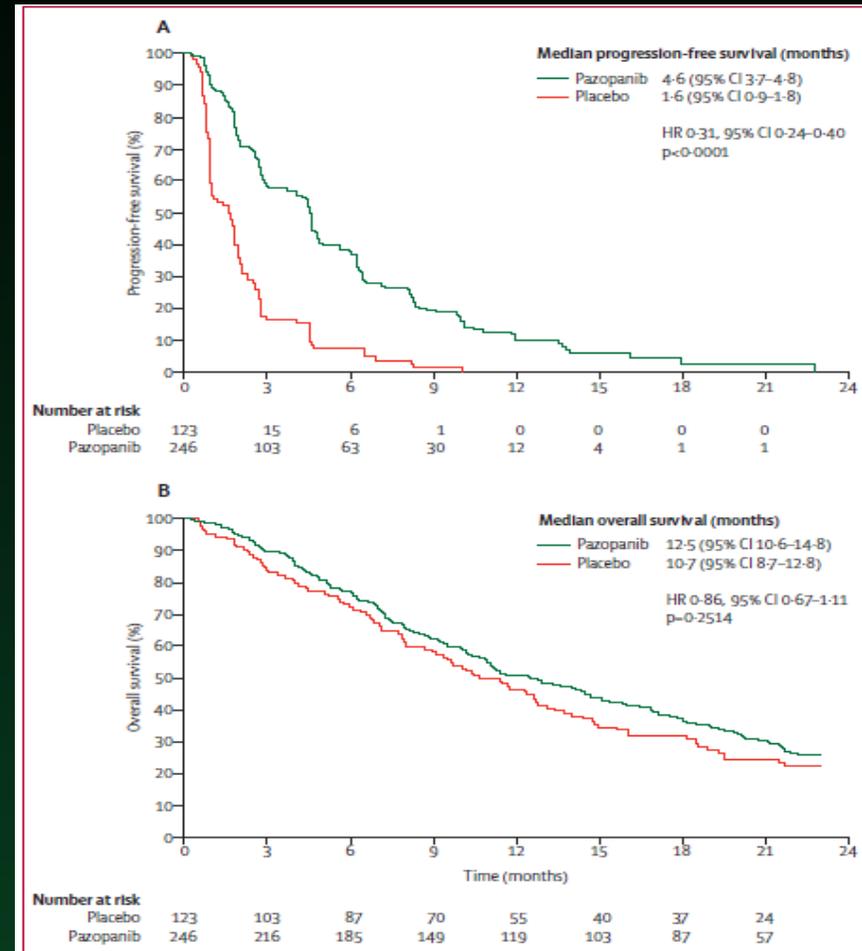
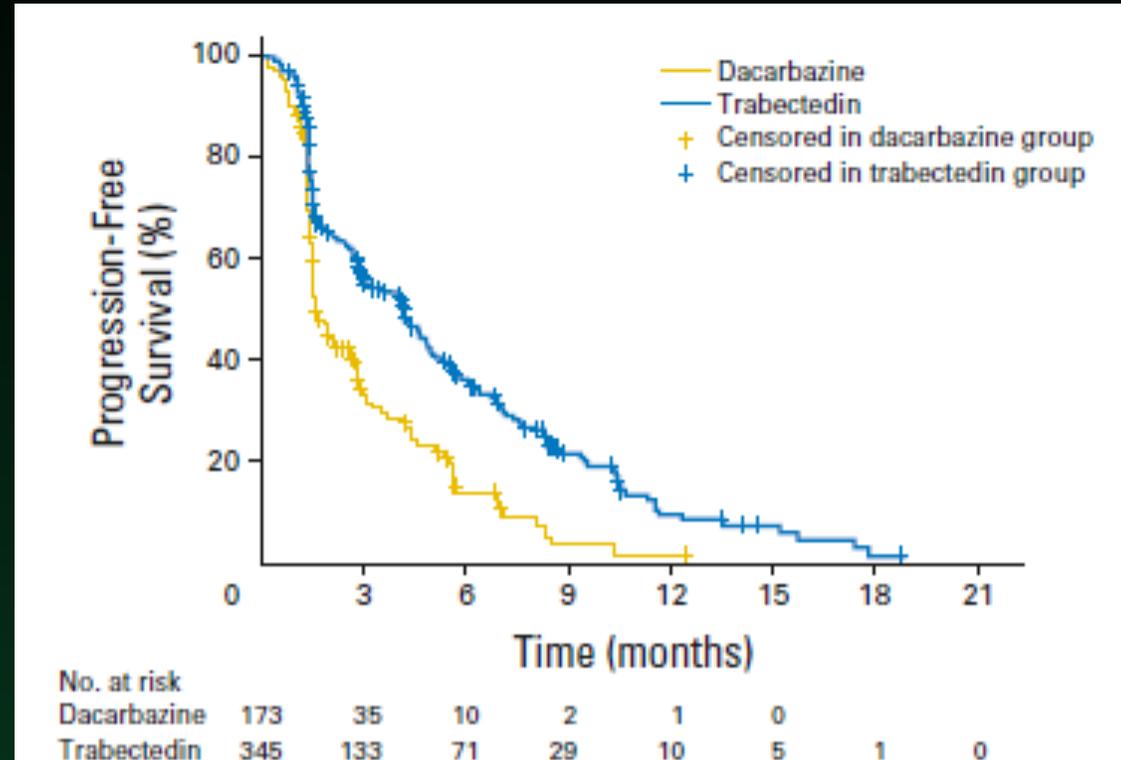


Figure 2: Kaplan-Meier curves for survival
Progression-free (A) and overall (B) survival. 106 patients died or had disease progression in the placebo group, 168 in the pazopanib group (cutoff Nov 22, 2010). 95 patients died in the placebo group, 185 in the pazopanib group (cutoff Oct 24, 2011).

HR = hazard ratio; CI = confidence interval.

Trabectedin vs Dacarbazine: PFS *Liposarcoma and Leiomyosarcoma*



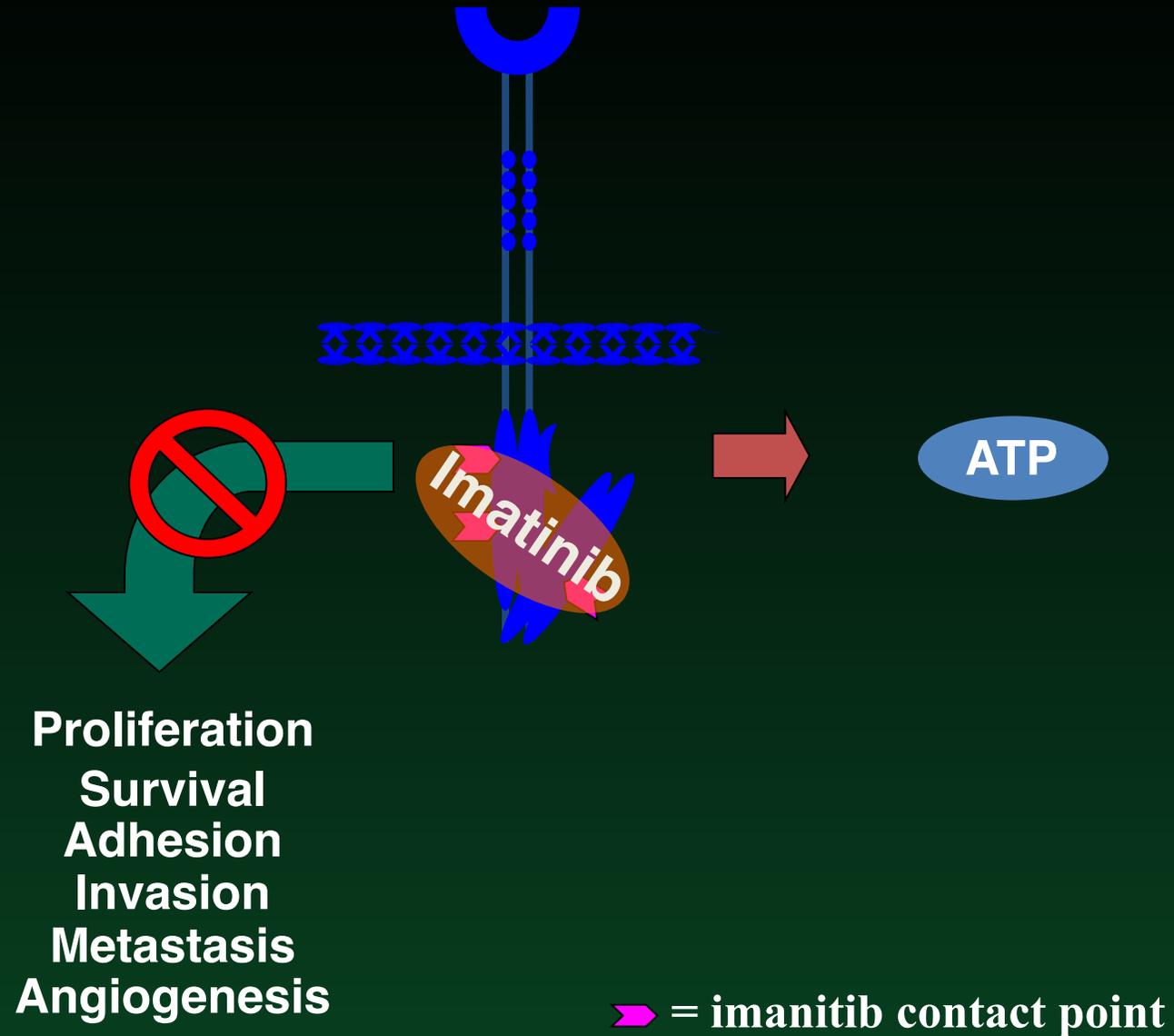
- PFRs at 3 and 6 months were 56% and 37% in the trabectedin arm versus 34% and 14% in the dacarbazine arm.

Precision Oncology

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)

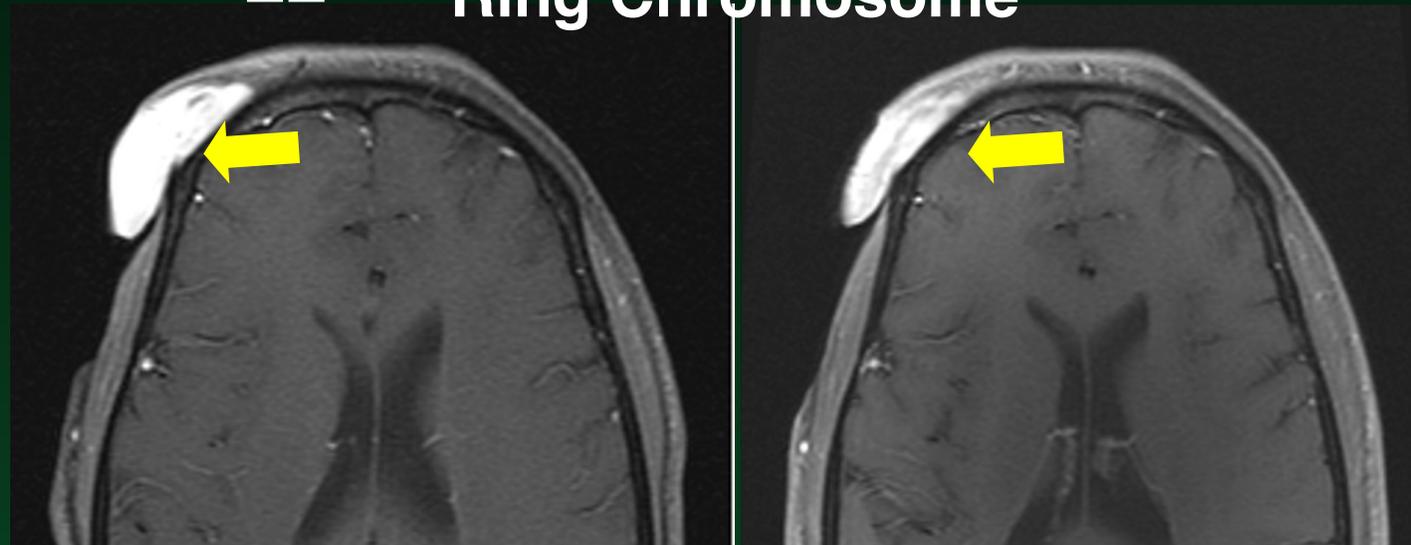
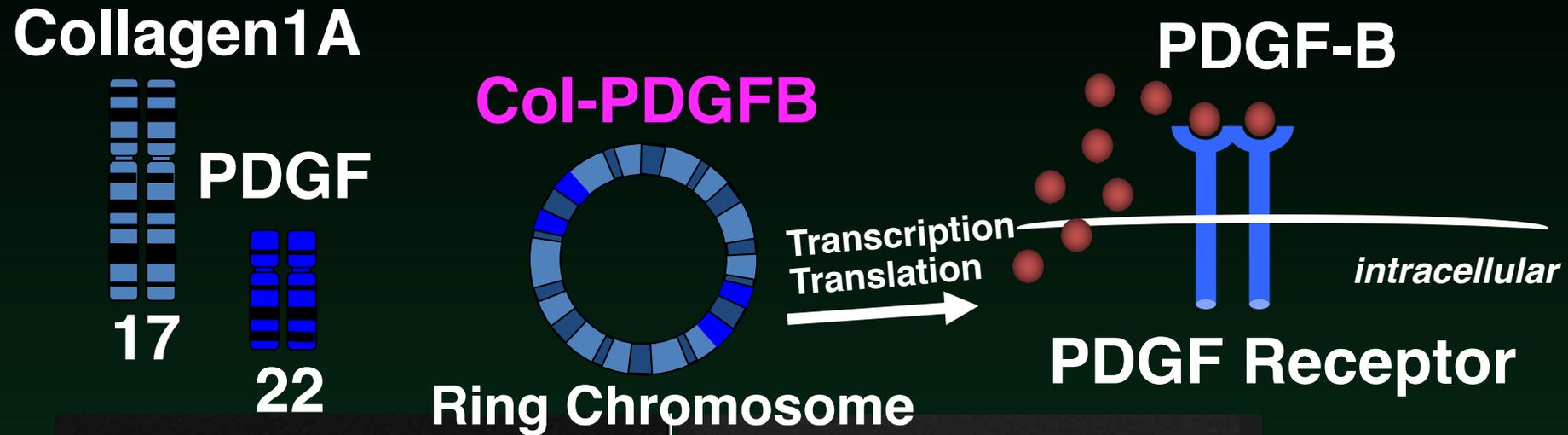
Kit Receptor Phenotype



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

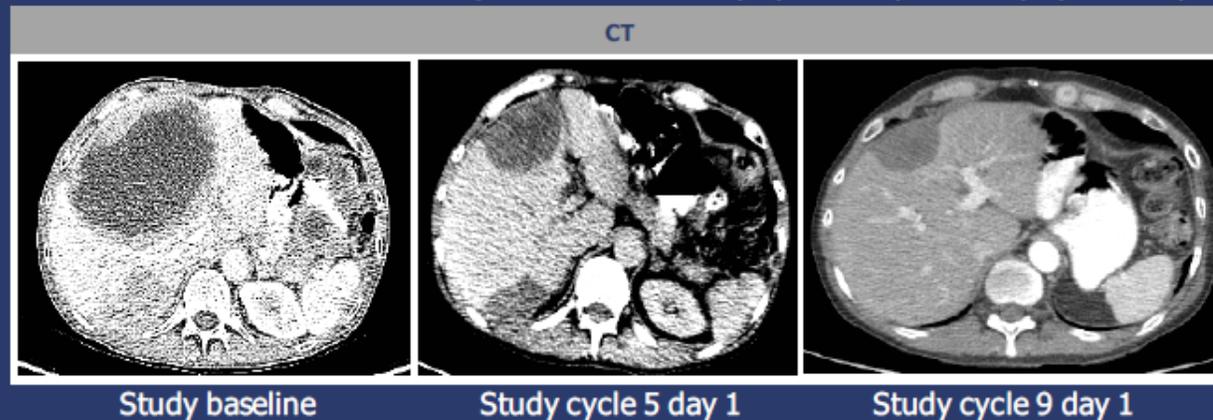
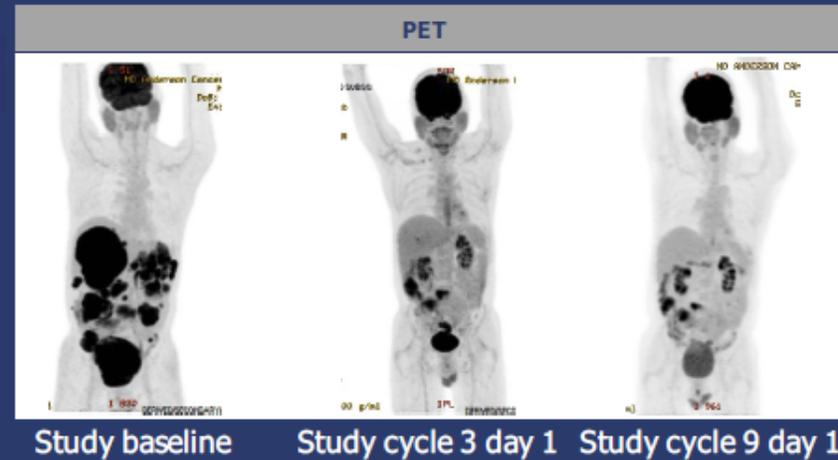
PDGFR Inhibitors in Dermatofibrosarcoma



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

Sarcoma With TRK Fusion

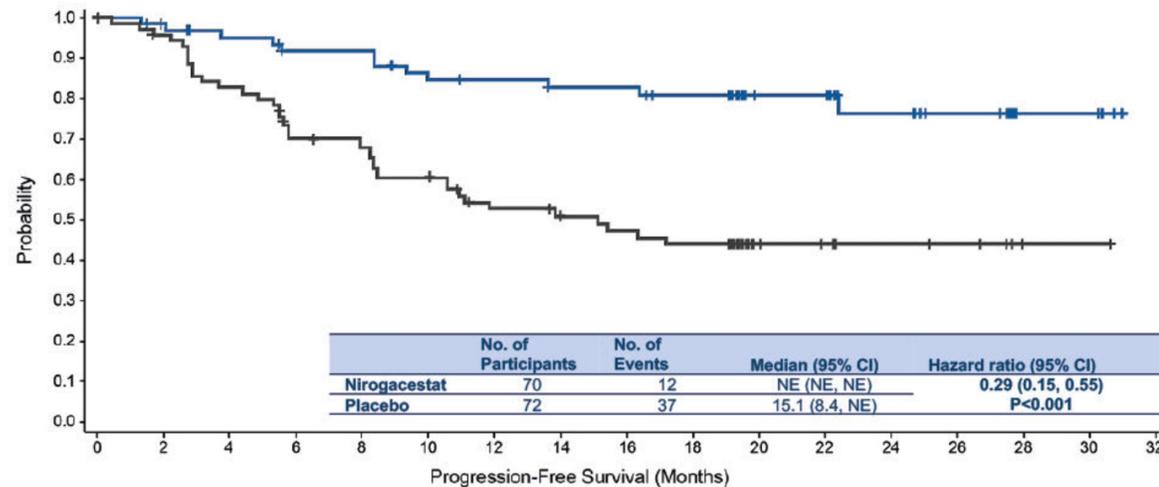
**Patient #2:
ETV6-NTRK3 fusion**



Phase 3 Niragacestat vs Placebo Desmoid Tumor

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

Nirogacestat significantly reduced risk of disease progression

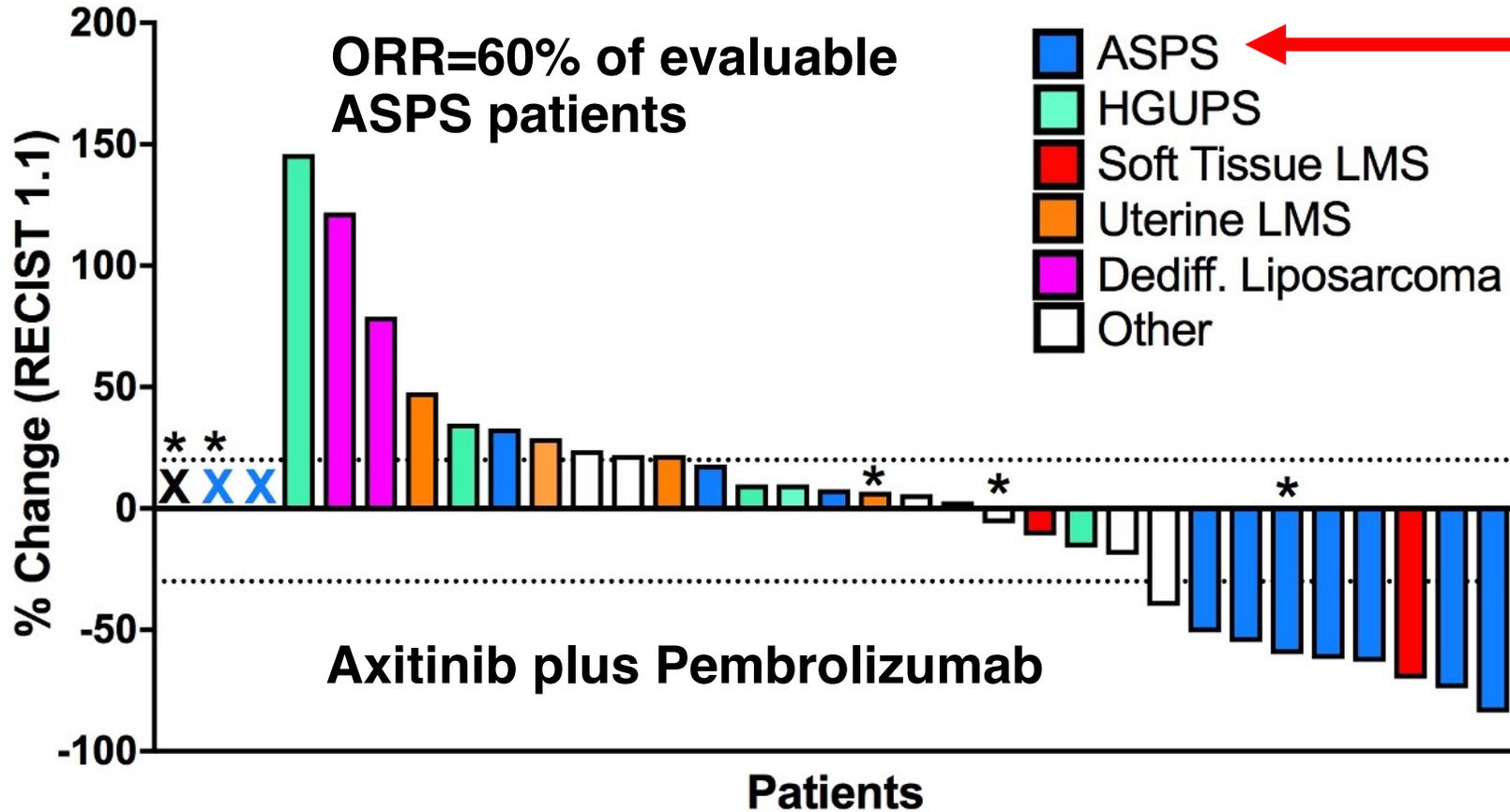


Median follow-up time was 19.2 months for nirogacestat and 10.9 months for placebo.
NE, not estimable.

Immunotherapy

Immune Checkpoint Inhibitors in Angiosarcoma

IN PURSUIT OF YOUR CURE.™



X - Non-evaluable for response imaging
 * - Non-target or clinical progression



TKI plus Immune Checkpoint Inhibitors in Alveolar Soft-part Sarcoma (ASPS)

IN PURSUIT OF YOUR CURE.™



Florou V, Rosenberg AE, Wieder E, Trent, et al Angiosarcoma patients treated with immune checkpoint inhibitors. *Journal for ImmunoTherapy of Cancer* 2019;7:213.

er Center

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, cytotoxic 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
 - 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
 - Yolanda Roper
- **Nursing**
 - Eryka Lacayo
 - Vilma Sanchez
 - Lila Wong
 - Amanda Martin
- **Social Work**
 - Marlene Morales
 - Adriana Alvaraez (AYA)
- **Orthopedic Oncology**
 - Fran Hornicek
 - Tom Temple
 - Sheila Conway
 - Frank Eismont
 - Juan Pretell
 - Mo Al Maaieh
- **Surgical Oncology**
 - Nipun Merchant
 - Alan Livingstone
 - Neha Goel
 - Dido Franceschi
- **Radiation Therapy**
 - Raphael Yechieli
 - Aaron Wolfson
 - Laura Freedman
- **Head & Neck Surgery**
 - Zoukaa Sargi
 - Frank Civantos
- **Thoracic Surgery**
 - Dao Nguyen
 - Nestor Villamizar
- **Interventional Radiology**
 - Shree Venkat
 - Prasoon Mohan
- **Gynecologic Oncology**
 - Matt Schlumbrecht
 - Marilyn Huang
- **Clinical Research**
 - Josefina Sanchez
 - Melissa Serna
 - Mirna Gonzalez
 - Karyms Luna
- **Lab Research**
 - Zhefeng Duan, PhD
 - Luyuan Li, PhD
 - Karina Galoian
 - Josie Eid, PhD
- **Fellows/Residents**
 - Andrea Espejo
 - Priscella Coelho
 - Phillipos Costa
 - Caroline Hana
 - Briana Valdes
 - Steven Bialick
 - Anthony Skyrd

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Diagnosis and Management

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