Sarcoma

Applying Molecular Medicine to Improve Outcomes

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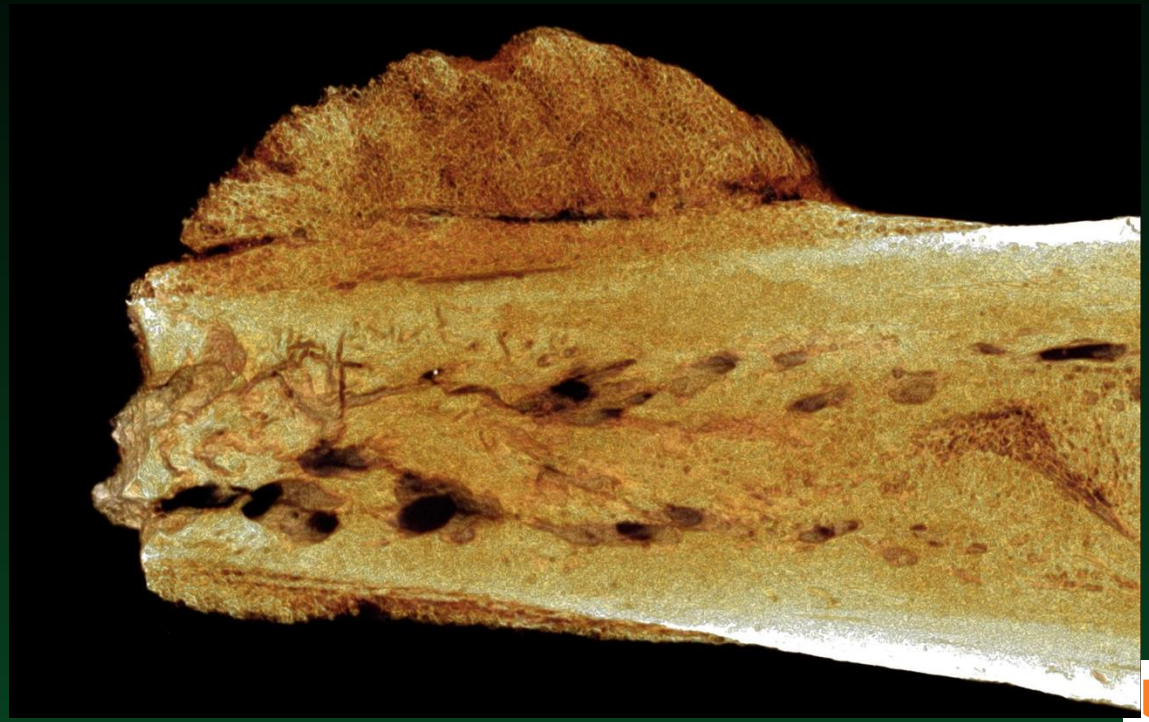
First Sarcoma (Osteosarcoma)

~1.7 million years ago



Randolph-Quinney, et al. SAJS, 2016

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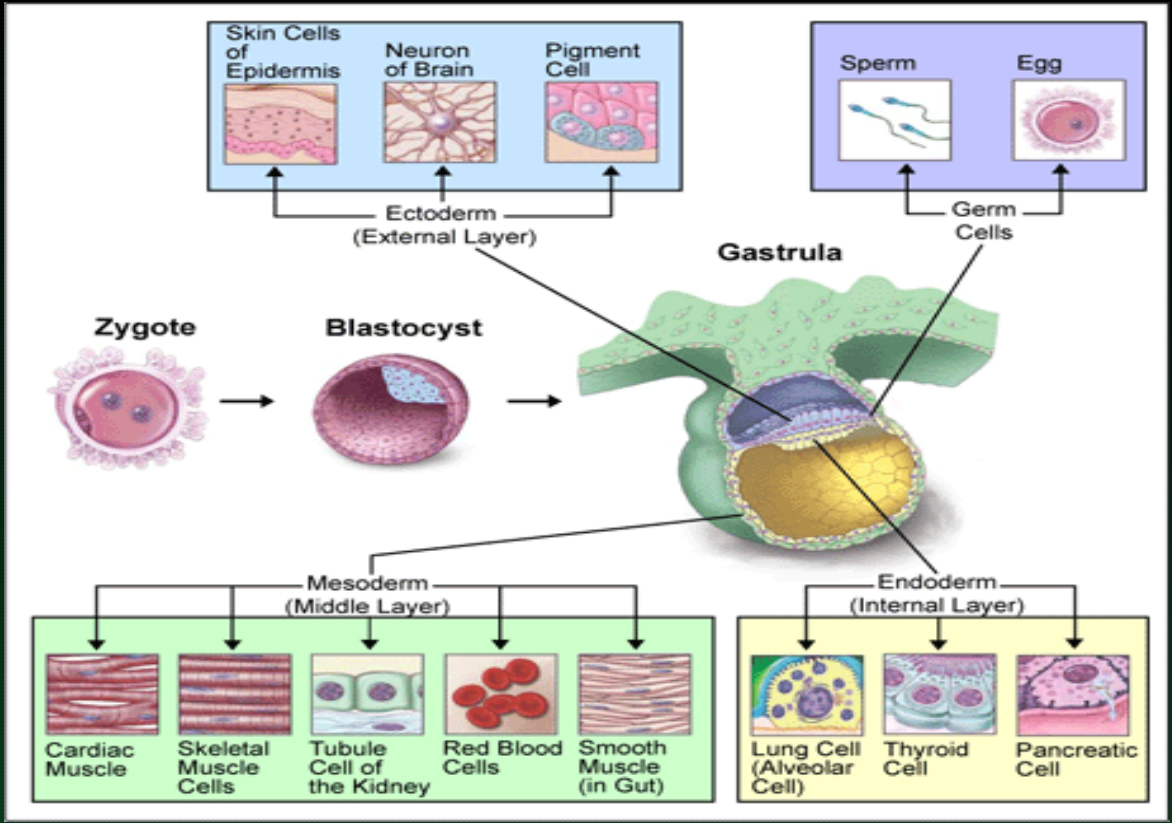

http://www.ncbi.nlm.nih.gov/About/primer/genetics_cell.html

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

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Anatomic Distribution

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

Diagnosis

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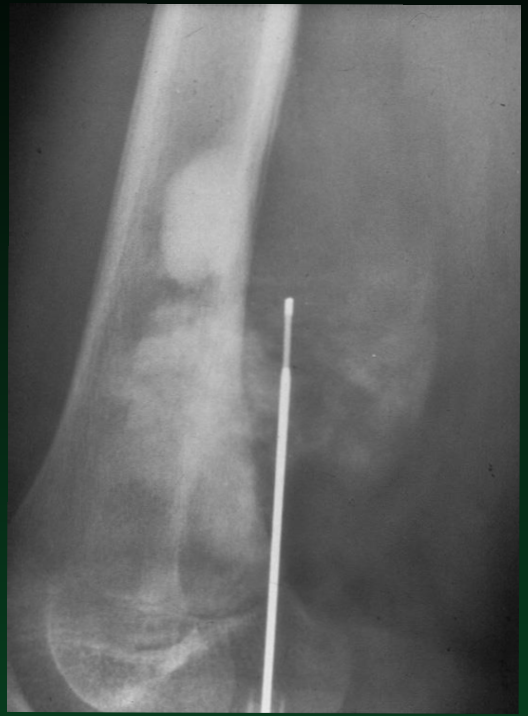
Tru-Cut (Core) Biopsy



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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.

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
- **Extraskeletal Bone Sarcomas**
  - Osteosarcoma
  - Ewing's Sarcoma Chondros

N=175

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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
- Eribulin

- Imatinib, sunitinib, regorafenib, ripretinib, avapritinib
- Pazopanib
- Pexidartinib, Vimseltinib
- Tazemetostat
- Denosumab
- Nab-sirolimus
- 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, 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

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%)

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 19:3483-89, 2004

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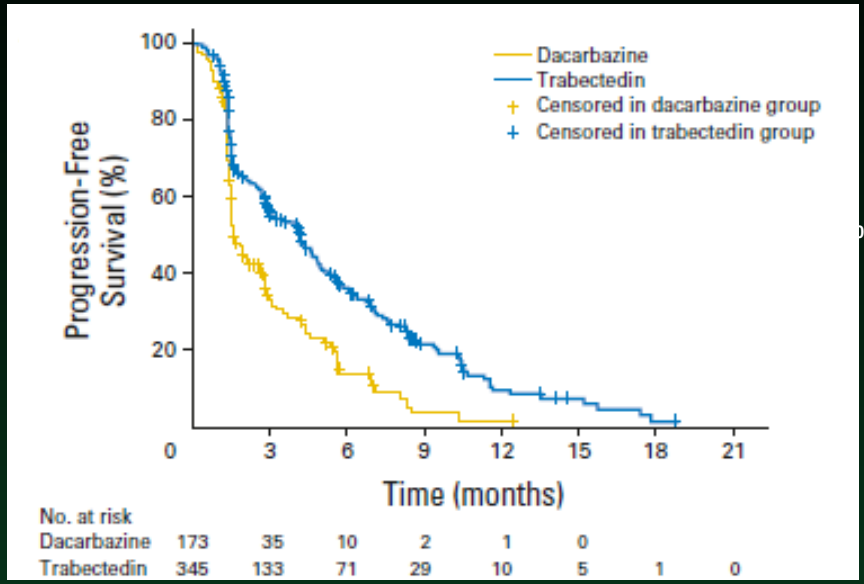
Trabectedin vs Dacarbazine: PFS
Liposarcoma and Leiomyosarcoma



01.

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

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

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).

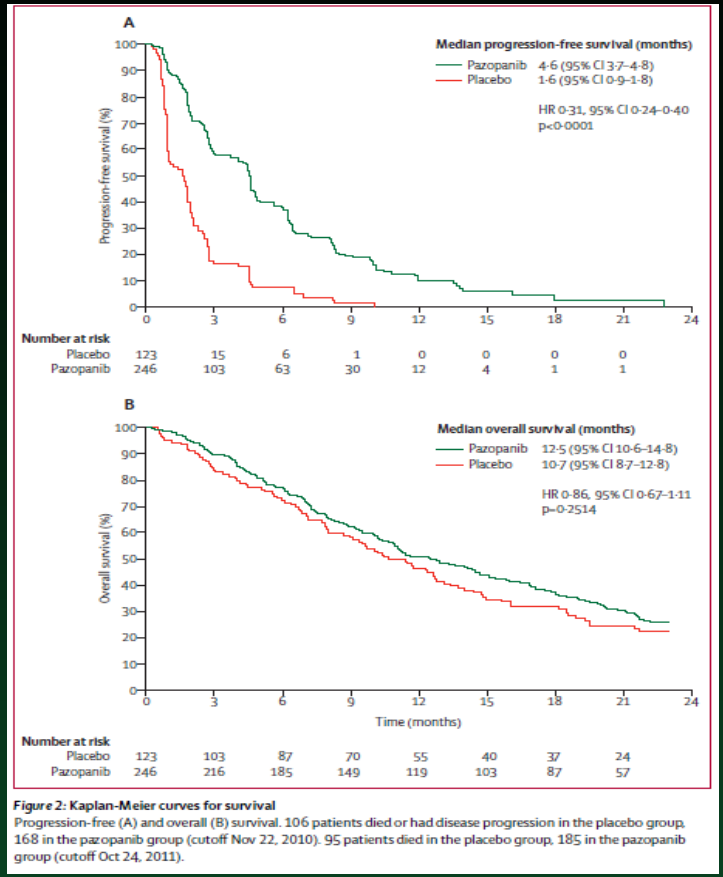


Figure 2: **Kaplan-Meier curves for survival**
Progression-free (A) and overall (B) survival. 106 patients died or had disease progression in the placebo group, 168 in the pazopanib group (cutoff Nov 22, 2010). 95 patients died in the placebo group, 185 in the pazopanib group (cutoff Oct 24, 2011).

HR = hazard ratio; CI = confidence interval.

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

Precision Oncology

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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)**

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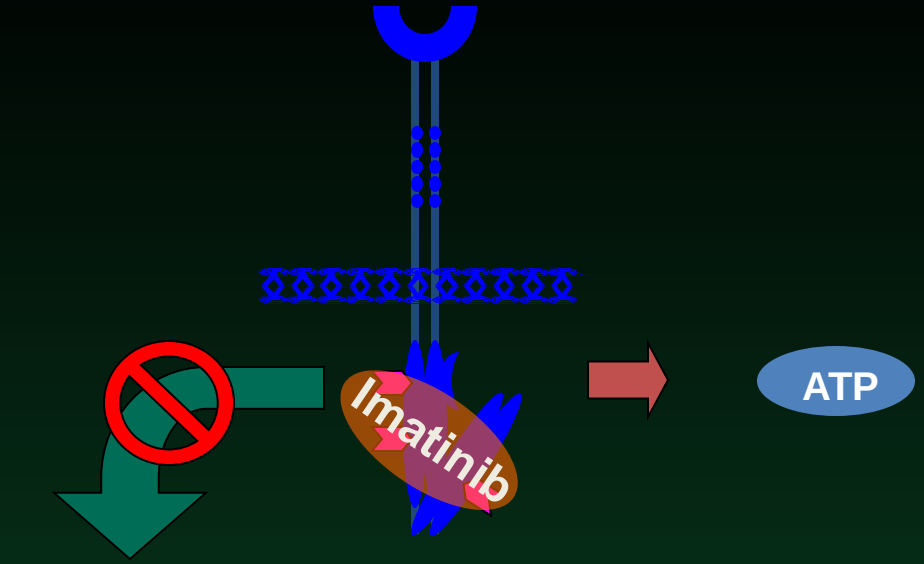
Kit Receptor Phenotype



Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

= imanitib contact point

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GIST Subtypes

Kit exon 11

Kit exon 9

KIT resistance mutations

Exon 13 (ATP binding site)

Exon 17 (A-loop)

PDGFR D842V

SDH deficiency

Raf V600E

NF-1, Ras

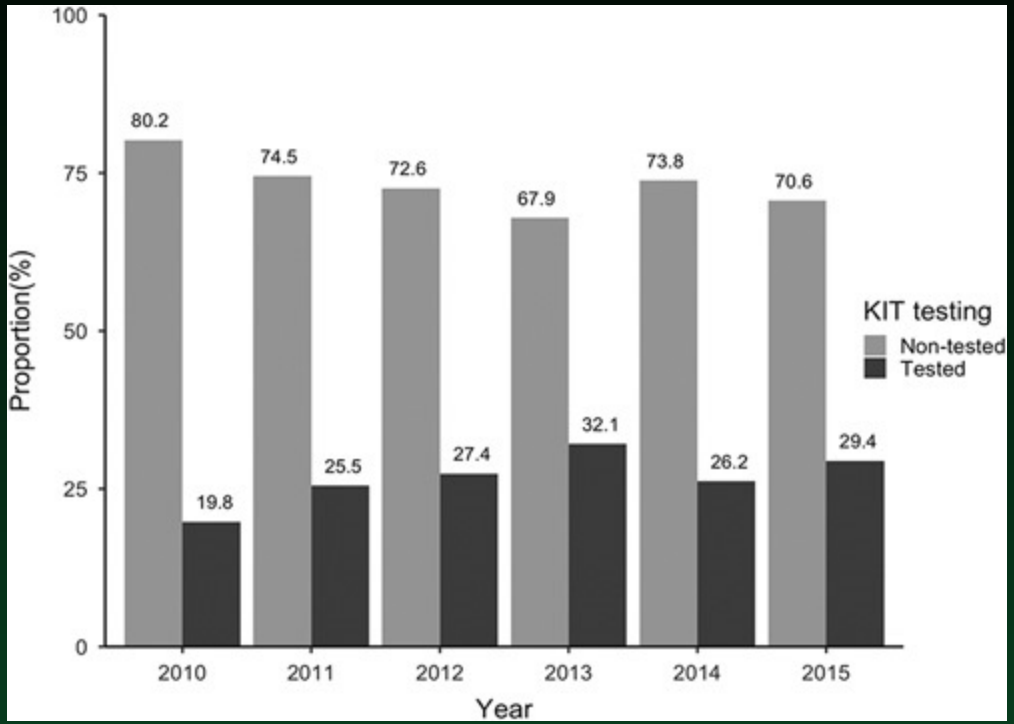
PI3K

IGF-1R expressing

TRK fusion

Jon Trent, MD, PhD

GIST mutation testing in US



Florindez and Trent. American Journal of Clinical Oncology, April 2020. 43 (4), 270-278. Low Frequency of Mutation Testing in the United States: An Analysis of 3866 GIST Patients

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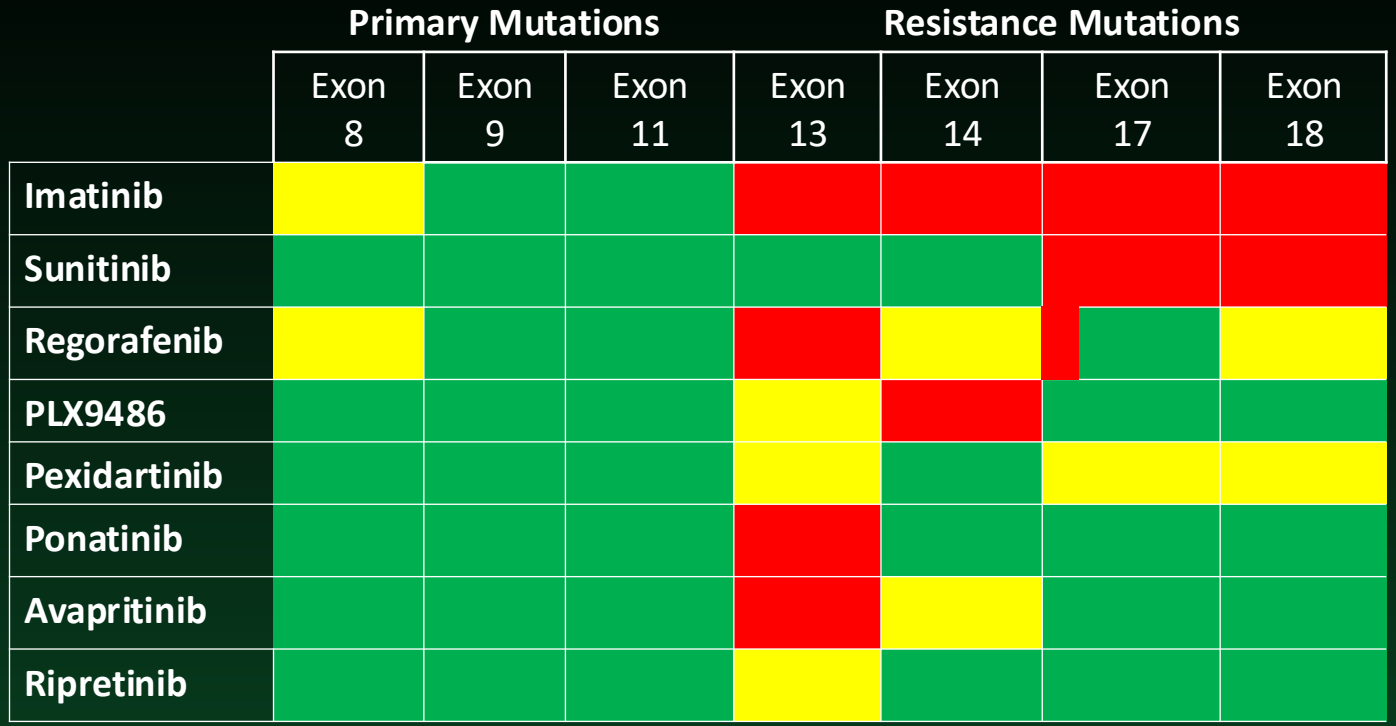
Differential Sensitivity to TKI



Junaid Arshad, Jonathan C. Trent. JCO Precision Oncology 2020 :4, 66-73

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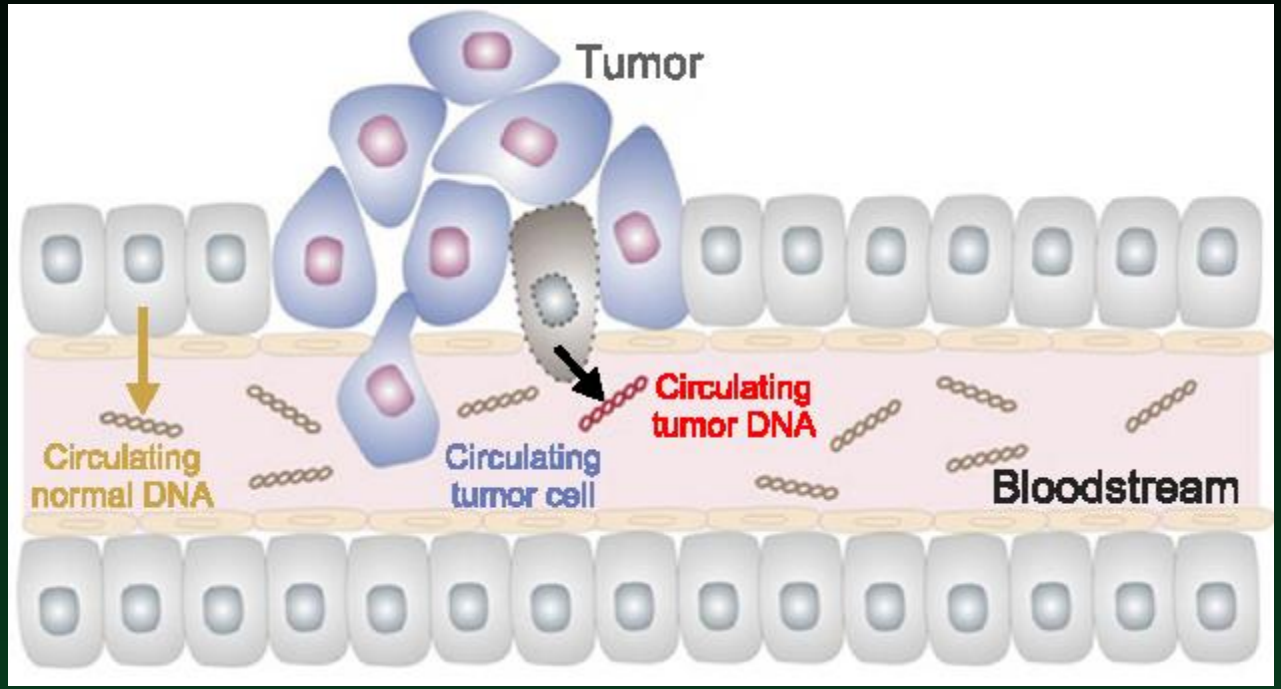
Circulating Tumor DNA

Mutation Testing From Blood (Liquid Biopsy)



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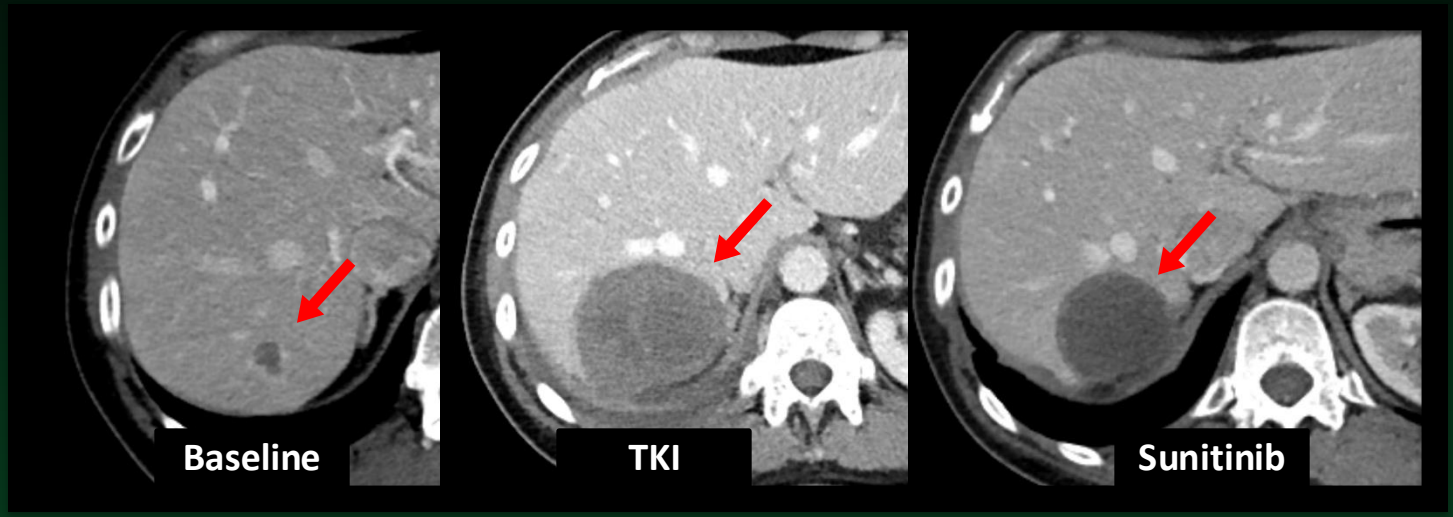
- 52 YO woman with small intestine, *KIT* exon 11 (L576P) mutant, GIST with liver metastases
- Response to imatinib durable for 2 years
- Progressive on imatinib placed on avapritinib, rapid progression
- ctDNA revealed *KIT* exon 13 V654A resistance mutation



Placed on sunitinib to target *KIT* exon 11 primary and *KIT* exon 13 resistance mutations

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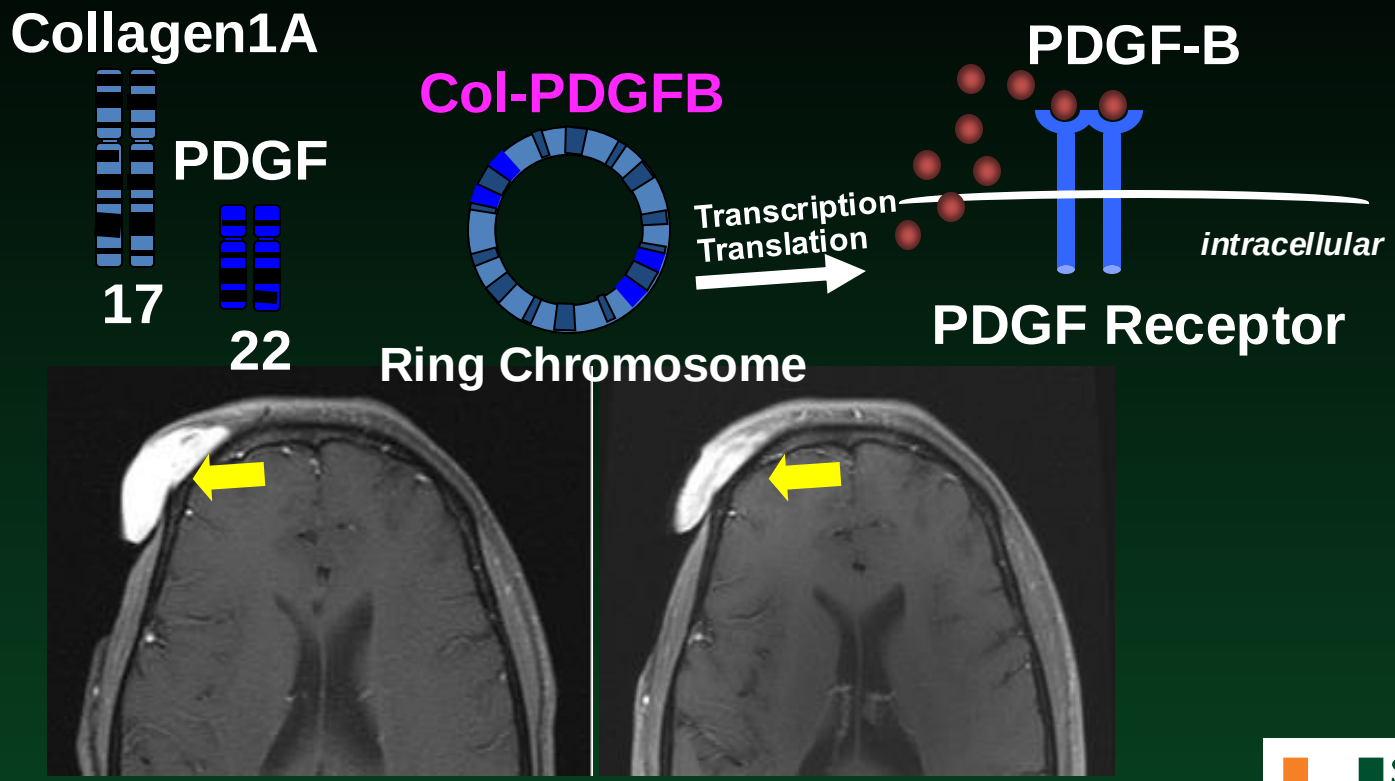
Junaid Arshad, Jonathan C. Trent. JCO Precision Oncology 2020 :4, 66-73

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

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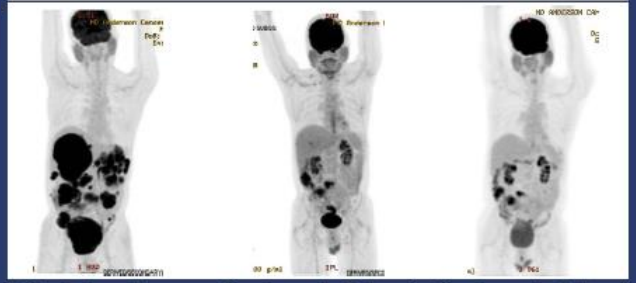
Sarcoma With TRK Fusion

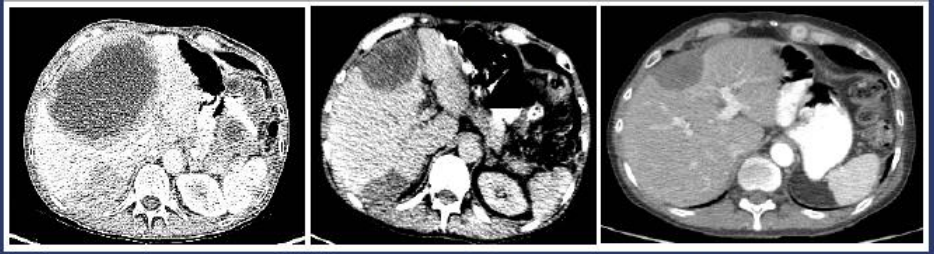
Patient #2:
ETV6-NTRK3 fusion

PET



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

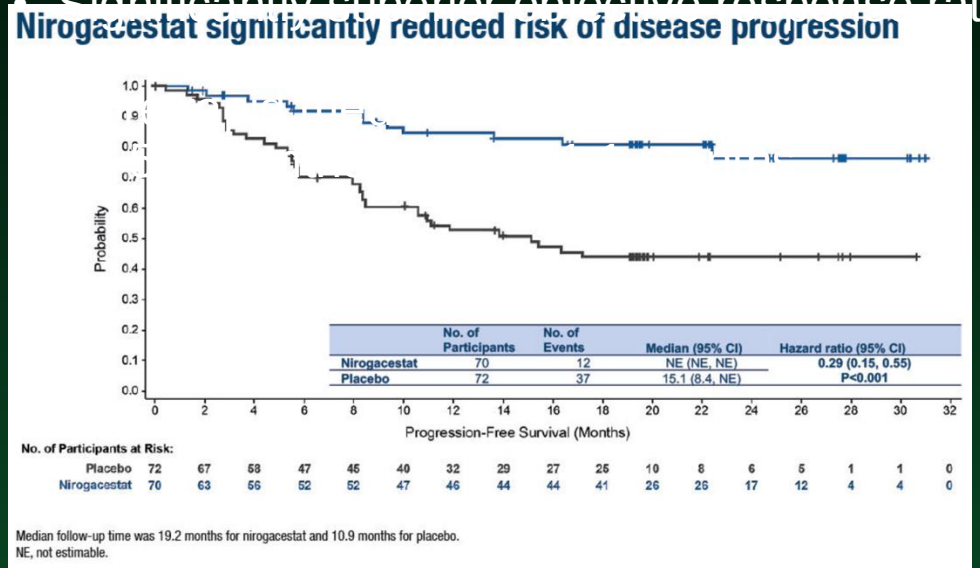
CT



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

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



ESMO 2022

Journal of Clinical Oncology > List of Issues > Volume 38, Issue 15 >

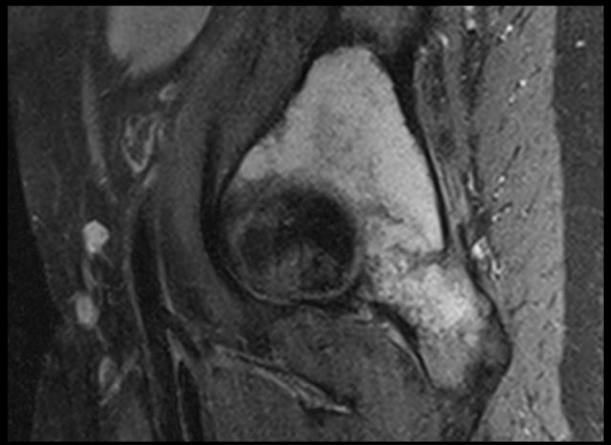
ORIGINAL REPORTS | Clinical Trials

Phase I Study of the Mutant IDH1 Inhibitor Ivosidenib: Safety and Clinical Activity in Patients With Advanced Chondrosarcoma

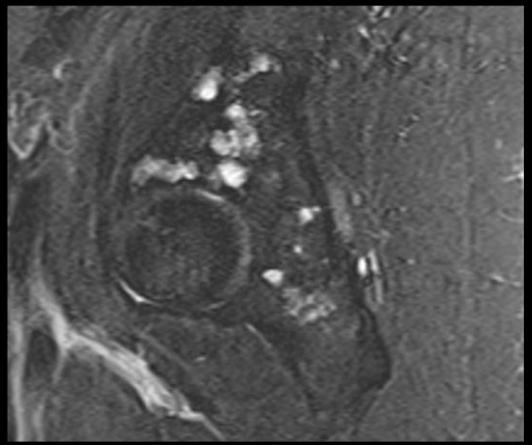
William D. Tap, MD[1,2]; Victor M. Villalobos, MD, PhD[3]; Gregory M. Cote, MD, PhD[4]; Howard Burris, MD[5]; Filip Janku, MD, PhD[6]; Olivier Mir, MD, MPH, PhD[7]; Murali Beeram, MD[8]; Andrew J. Wagner, MD, PhD[9]; Liewen Jiang, PhD[10]; Bin Wu, PhD[10]; Sung Choe, PhD[10]; Katharine Yen, PhD[10]; Camelia Gliser, BS[10]; Bin Fan, PhD[10]; Sam Agresta, MD, MPH[10]; Shuchi S. Pandya, MD[10]; and Jonathan C. Trent, MD, PhD[11]

MRI Response of Chondrosarcoma To IDH Inhibitor

MRI With Contrast



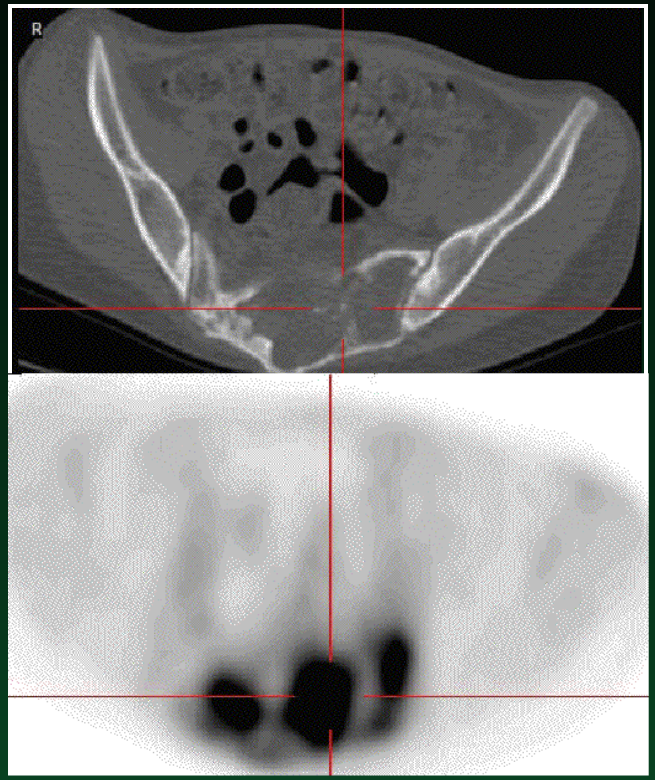
MRI With Contrast



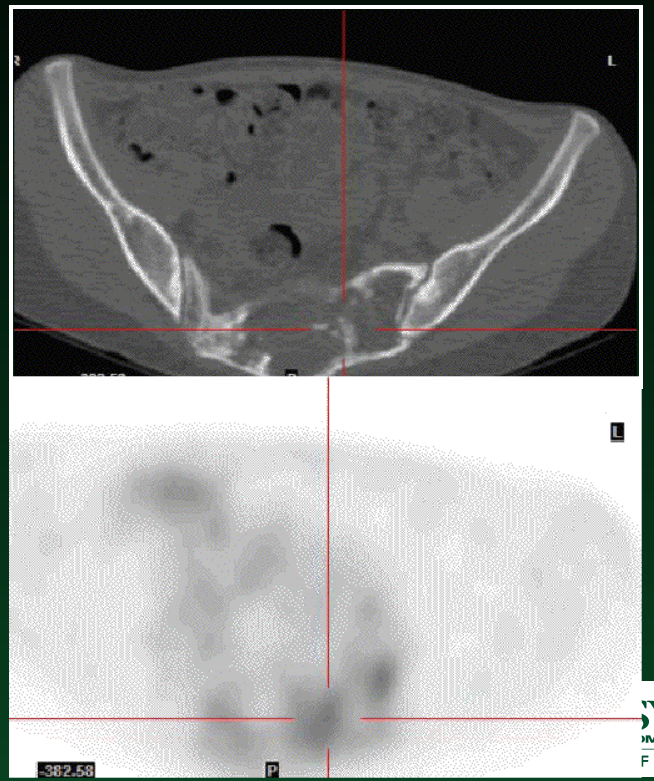
Personal Communication Jon Trent, MD, PhD

Radiologic Response to Denosumab

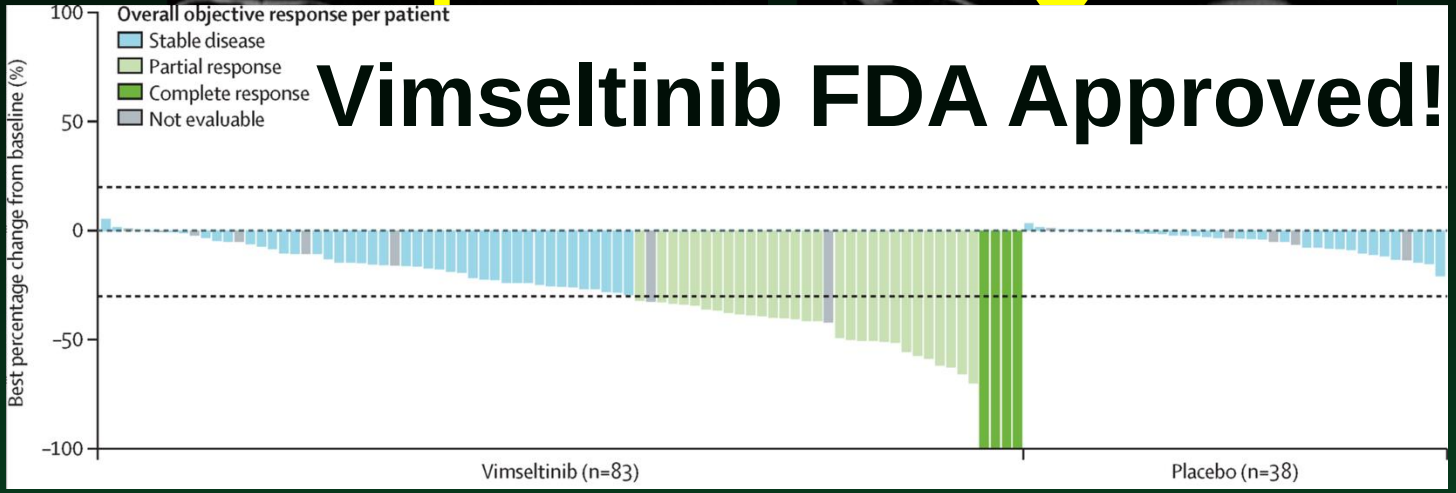
Pre-Treatment



Week 13 Post-Treatment



Pexidartinib Can Produce Significant Response in TGCT



Vimseltinib FDA Approved!

This patient underwent margin negative resection and remains free of disease at 22 months off pexidartinib

Personal Communication, J Trent

The Lancet, Volume 403, Issue 10445, 2709 - 2719

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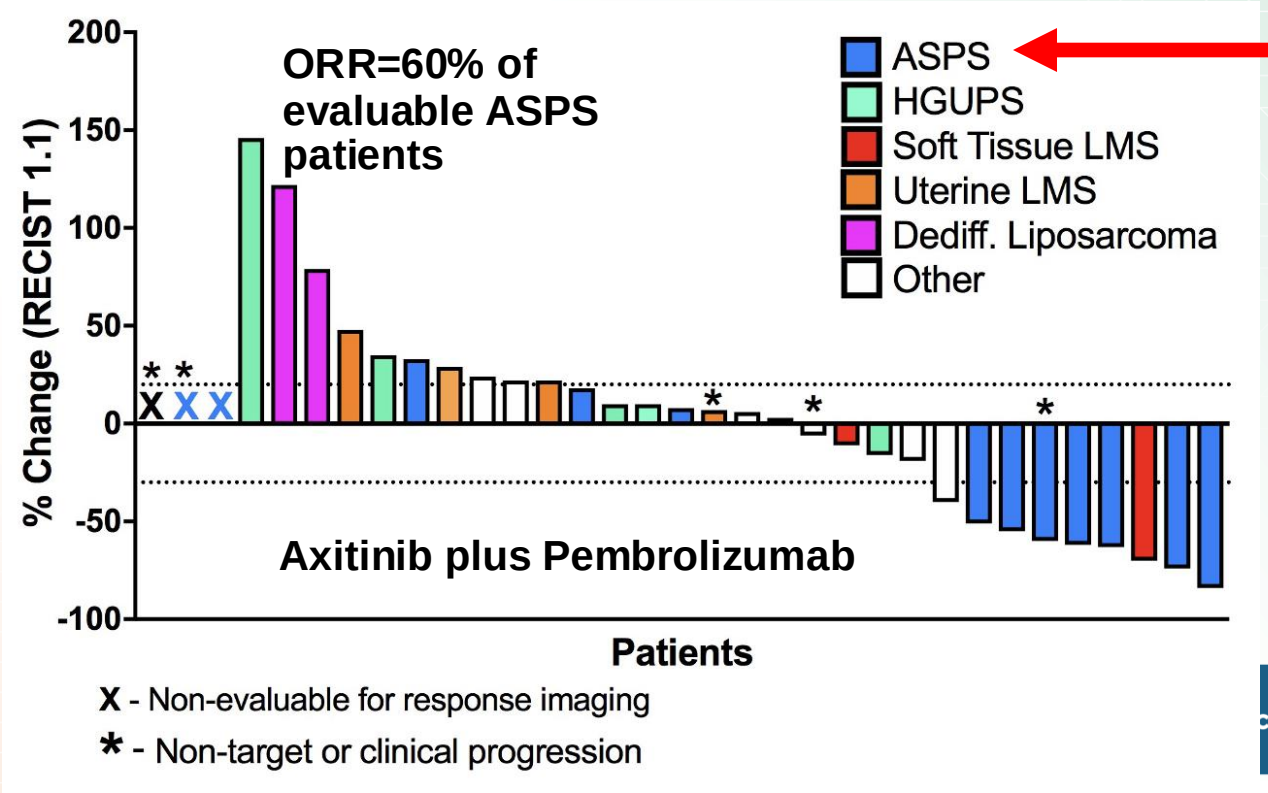
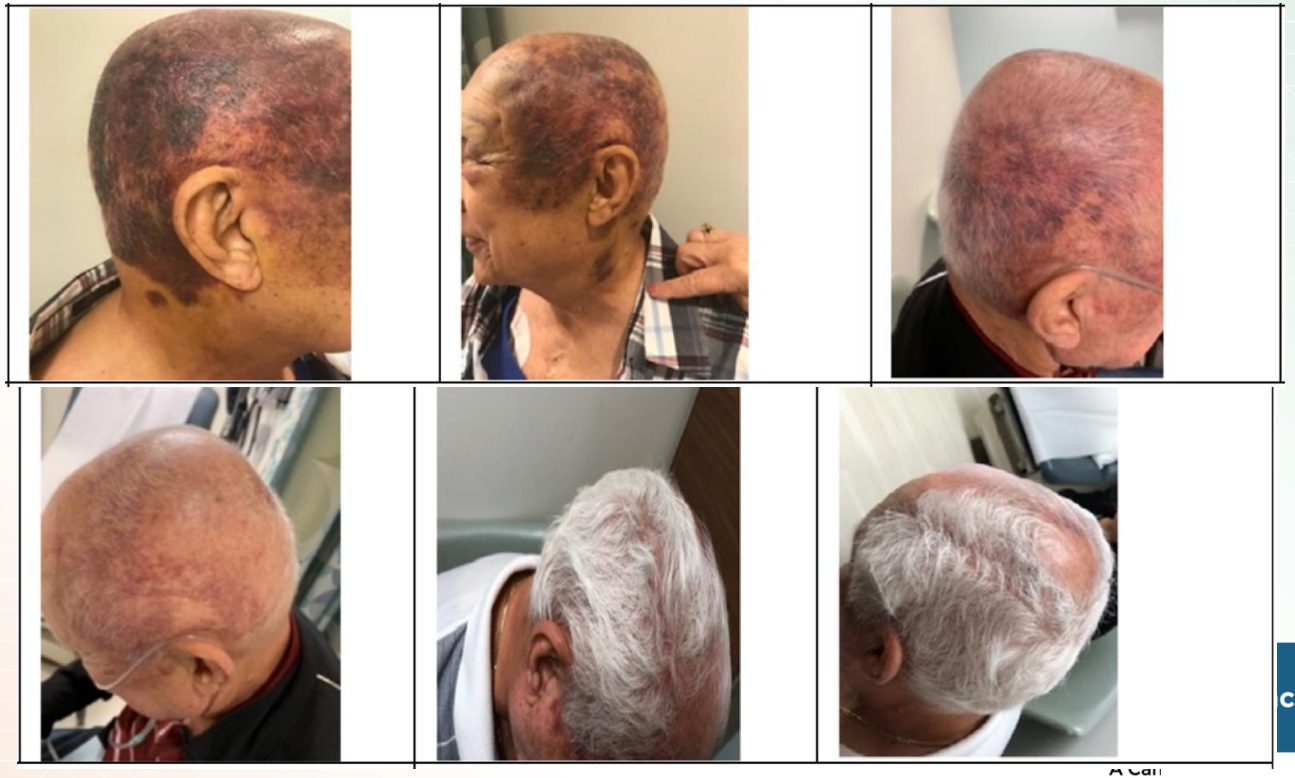
Immunotherapy

Immune Checkpoint Inhibitors in Alveolar Soft Part Sarcoma (ASPS)



Wilky,.... Trent. Lancet Oncol. 2019 Jun;20(6):837-848. doi: 10.1016/S1470-2045(19)30153-6

TKI plus Immune Checkpoint Inhibitors in Angiosarcoma



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

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

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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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Bone and Soft-tissue Sarcomas

Diagnosis and Management

Jon Trent, MD, PhD

Professor of Medicine
Director, Bone and Soft-tissue Sarcoma
Associate Director, Clinical Research
The University of Miami,
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