Fred Hutch Cancer Center

Oncology Board Review: Sarcoma

Min S. Park, MD
Clinical Associate Professor, Division of Hematology/Oncology, UW SOM
Clinical Director, Sarcoma Medical Oncology, Fred Hutch Cancer Center
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UW Medicine

Disclosures

- Stocks or stock options – Ely Lilly, Johnson & Johnson, Thermo Fisher Scientific

Learning Objectives

- Understand key management principles of patients with localized and metastatic soft tissue sarcoma
- Understand risk stratification for patients with resected GIST and systemic therapy for metastatic GIST
- Identify sarcoma subtypes that require multimodality therapy

Overview

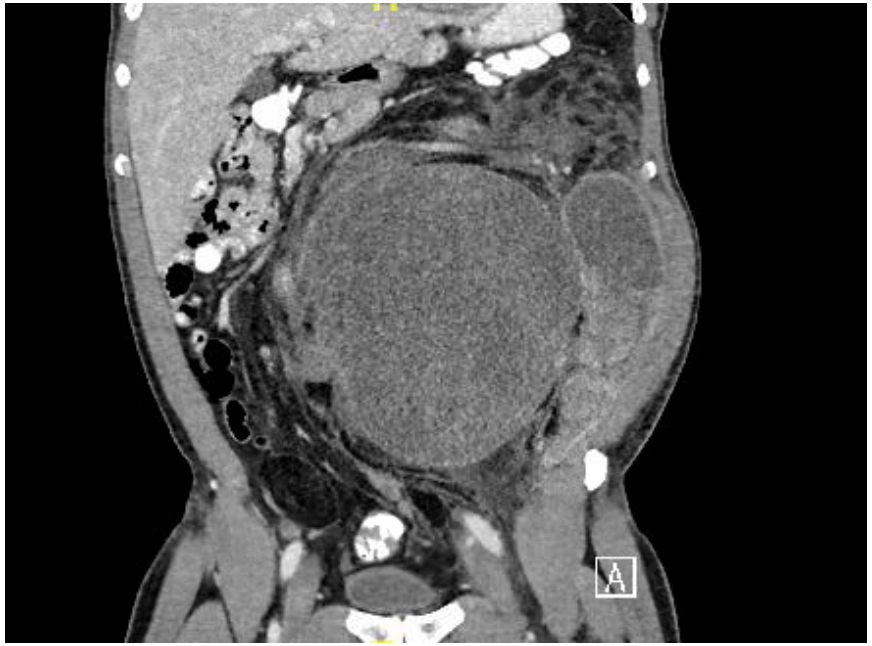
- Soft Tissue Sarcoma - Neoadjuvant/adjuvant therapy
- Soft Tissue Sarcoma - Metastatic disease
- GIST
- Bone Sarcomas/other

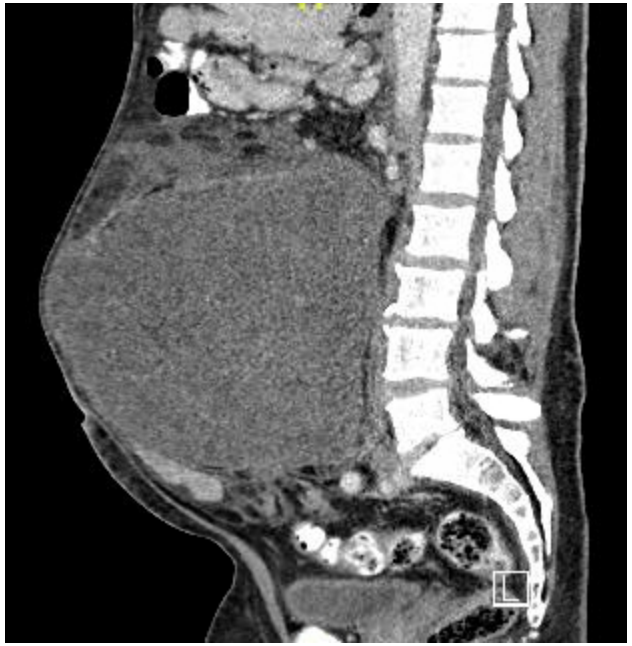
Case Presentation 1

- **55M presents with large abdominal mass over the past ~6 months**
- **Previously healthy, no significant PMH**
- **Labs normal**

Slide adapted from M Wagner

Case Presentation 1





- Pathology: Dedifferentiated liposarcoma
- CT chest: no metastatic disease

Slide adapted from M Wagner

Overview

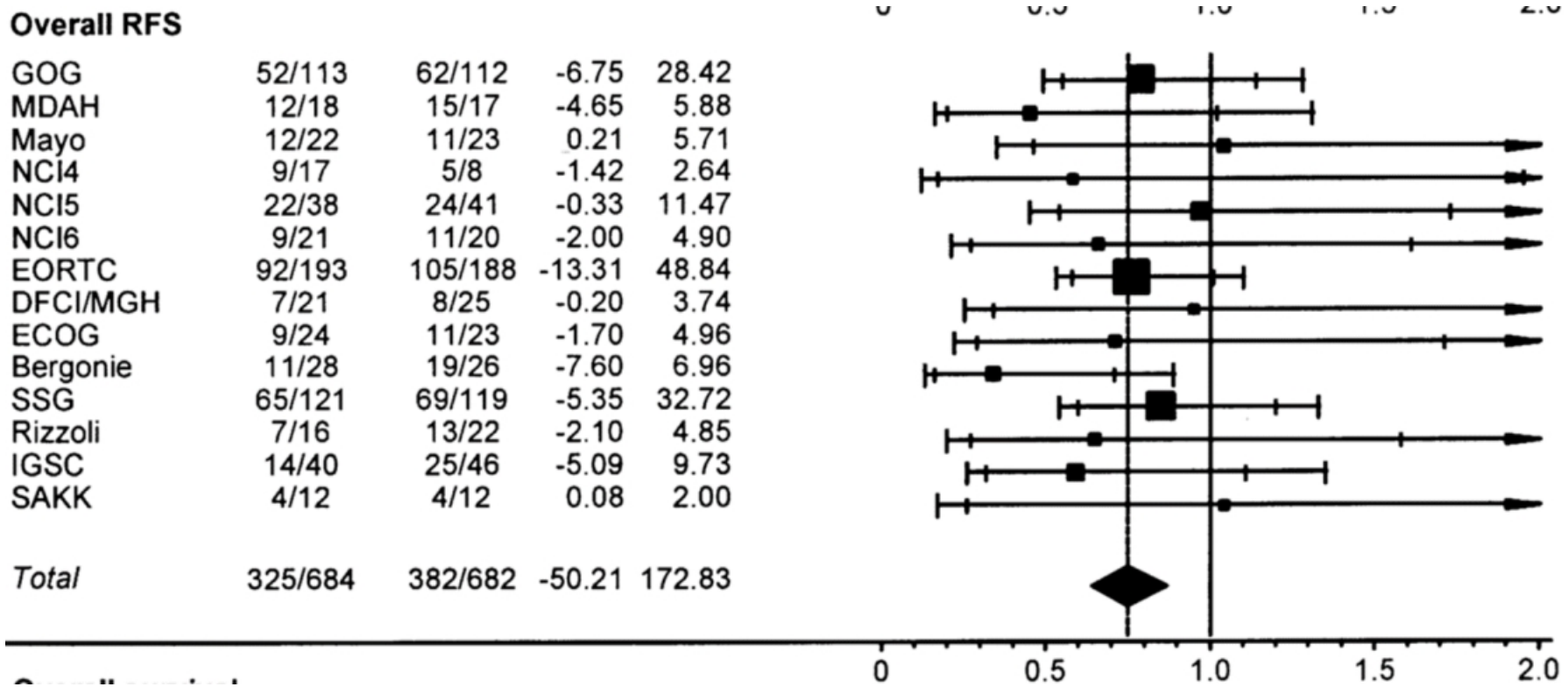
- **Soft Tissue Sarcoma - Neoadjuvant/adjuvant therapy**
- Soft Tissue Sarcoma - Metastatic disease
- GIST
- Bone/other

Treatment of localized STS

- Patients with an inadequate initial surgery have a higher rate of distant metastatic disease
- Wide local excision without transecting tumor is important
- Limb sparing surgery is the standard of care in most cases for extremity STS/bone sarcoma
- Large, high grade extremity STS need neo/adj XRT for local control
- Less clear for RP and abdominal sarcomas
  - Usually a case by case assessment- STRASS trial arguing against routine preoperative RT in RP sarcomas

Slide adapted from R Ratan, M Wagner

Adjuvant chemotherapy in STS

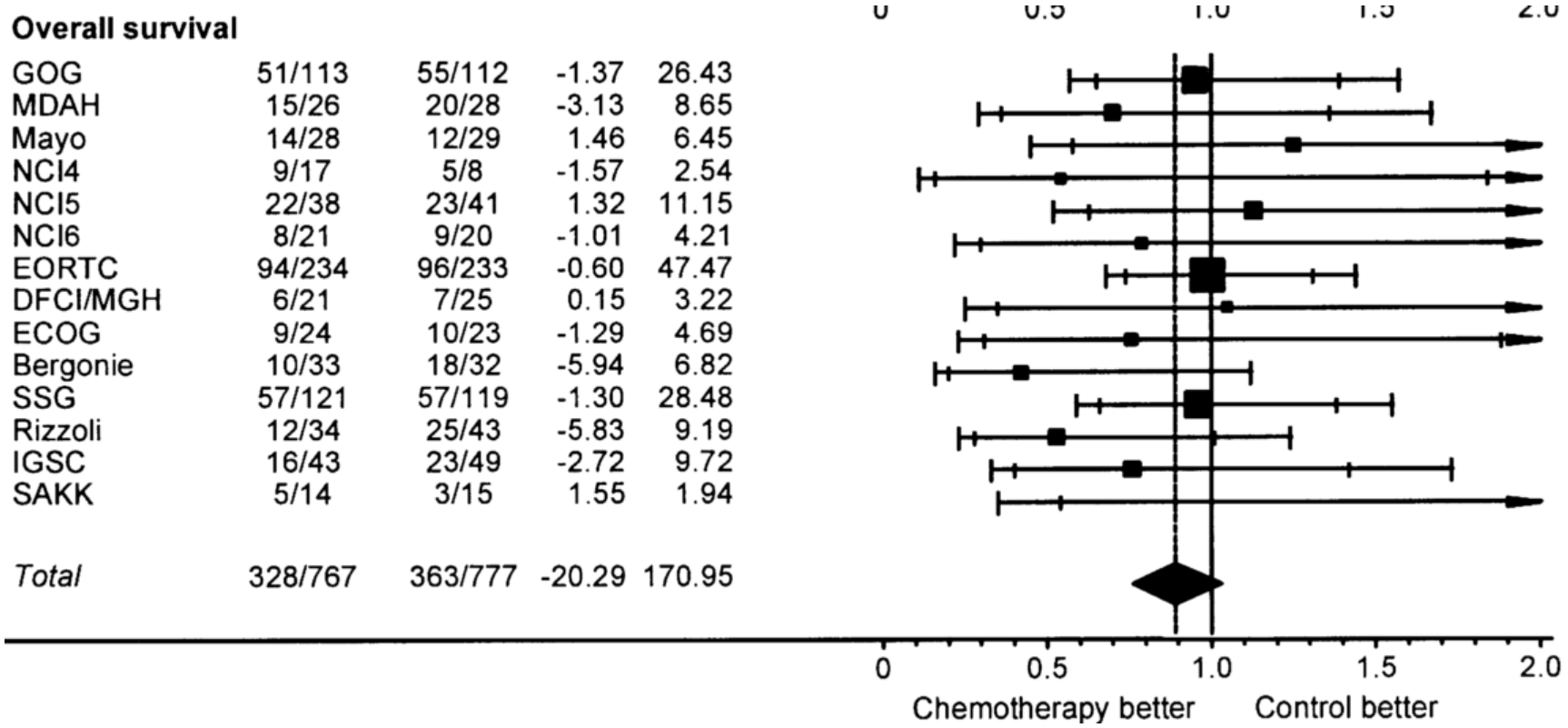


Overall RFS				
GOG	52/113	62/112	-6.75	28.42
MDAH	12/18	15/17	-4.65	5.88
Mayo	12/22	11/23	0.21	5.71
NCI4	9/17	5/8	-1.42	2.64
NCI5	22/38	24/41	-0.33	11.47
NCI6	9/21	11/20	-2.00	4.90
EORTC	92/193	105/188	-13.31	48.84
DFCI/MGH	7/21	8/25	-0.20	3.74
ECOG	9/24	11/23	-1.70	4.96
Bergonie	11/28	19/26	-7.60	6.96
SSG	65/121	69/119	-5.35	32.72
Rizzoli	7/16	13/22	-2.10	4.85
IGSC	14/40	25/46	-5.09	9.73
SAKK	4/12	4/12	0.08	2.00
Total	325/684	382/682	-50.21	172.83

- **Improvement in RFS**

SMAC, Lancet 1997

Adjuvant chemotherapy in STS



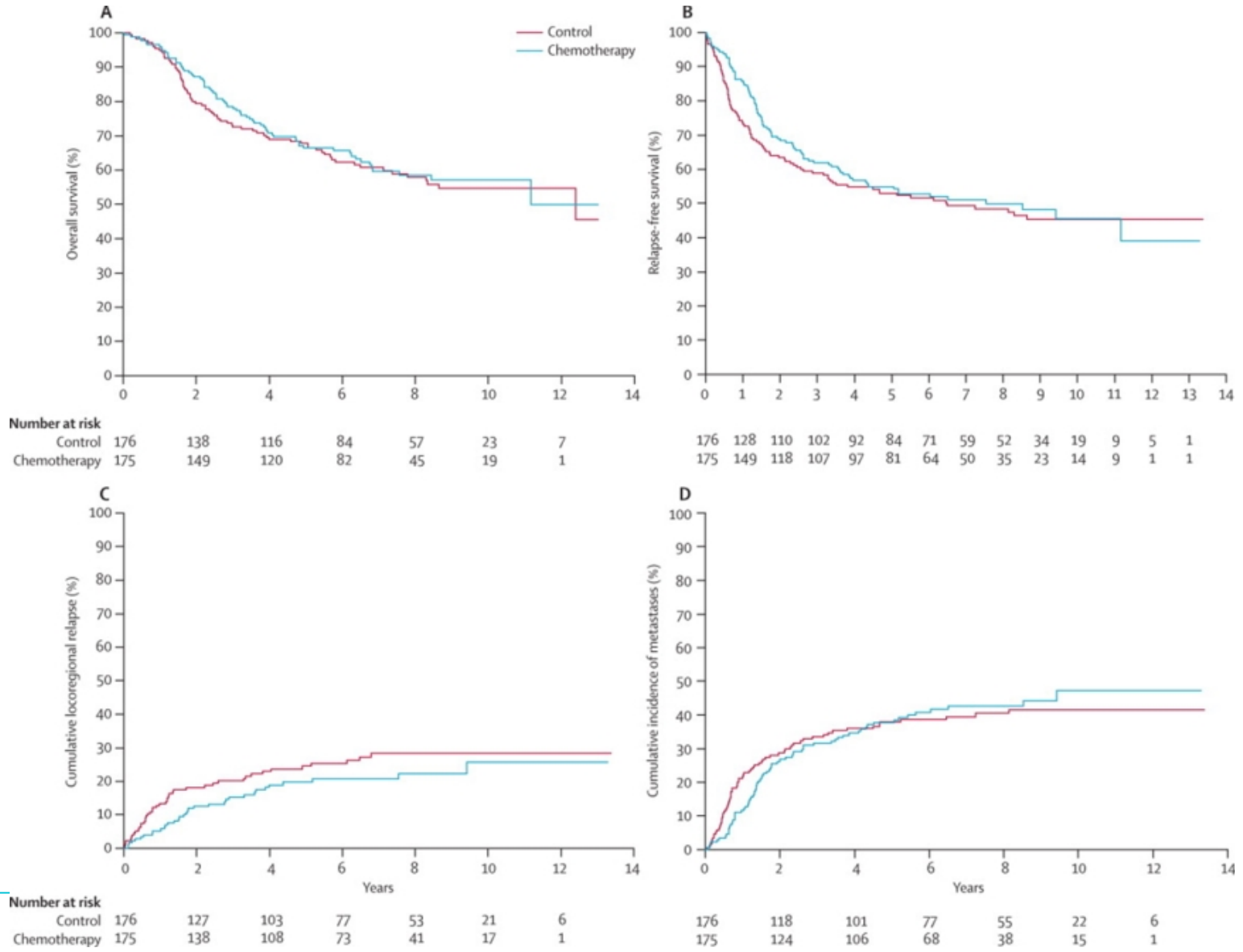
- **Trend but not significant improvement in OS**

SMAC, Lancet 1997

Adjuvant chemotherapy: EORTC 62931 study

- Randomized
- Doxo 75 + Ifos 5
  Vs no chemo
- Grade 2 and 3 Dz
- All pts had surgery
  +/- RT as per SOC

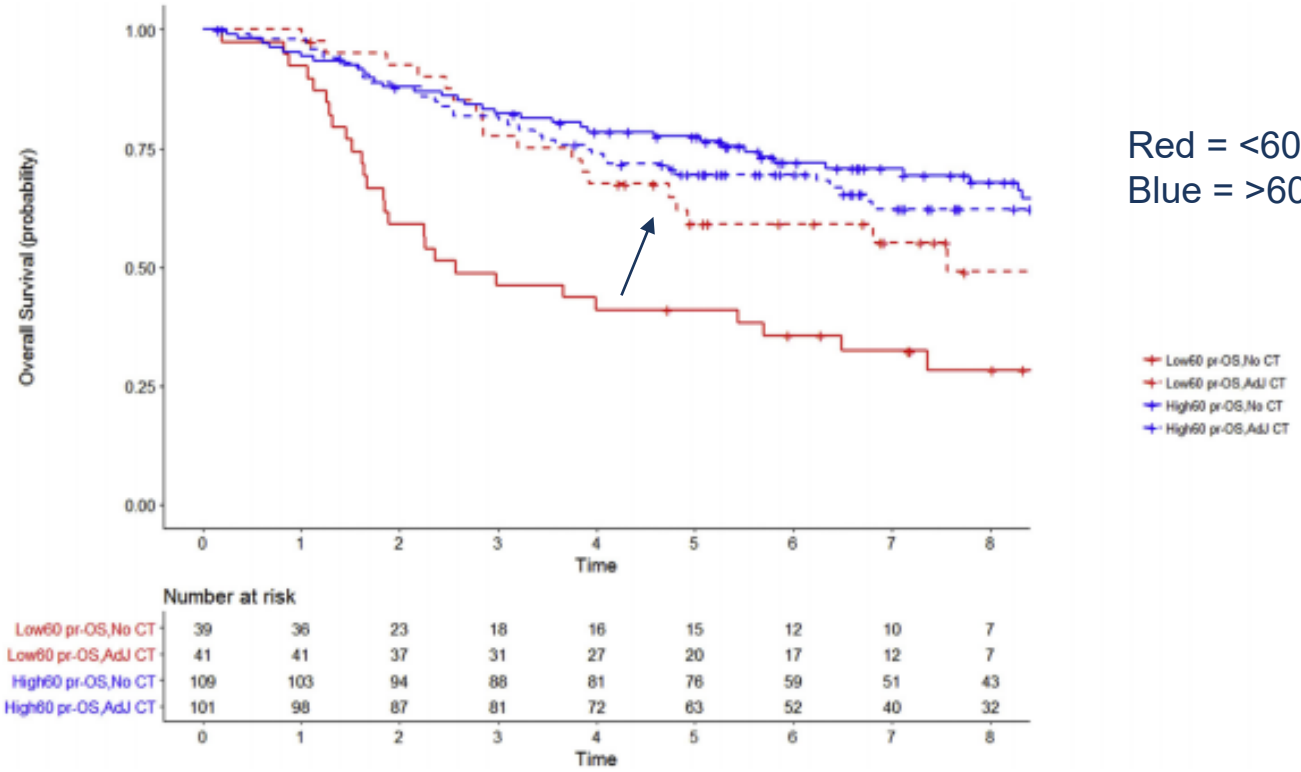
- Trend towards but non significant OS benefit (the primary endpoint)



Woll et al, Lancet Onc 2012

Can patients most likely to benefit from neo/adj chemoRx be identified?

- Stratification by pts with 10-year predicted OS: 60%



Red = <60% prob survival
Blue = >60 % prob survival

- Chemotherapy improves OS of highest risk patients

Pasquali et al, EJC, 2019

Neo/adjuvant chemotherapy: summary of sarcoma metanalysis consortium

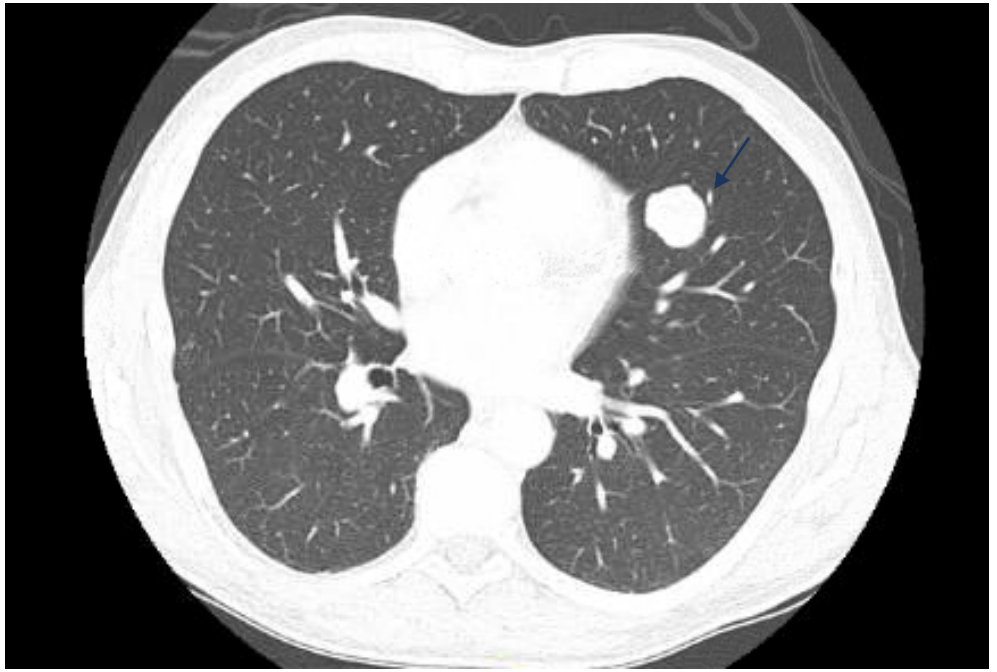
- Adjuvant chemo improved relapse free survival
- No significant benefit in OS
- Controversial because many argue sub-par chemo dosing and poor patient selection
- Updates after this meta-analysis failed to provide clear, universal guidance
- *Board answer: No adjuvant chemoRx

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Neoadjuvant/ Adjuvant Therapy	• AIM (doxorubicin, ifosfamide, mesna)[1-4] • Ifosfamide, epirubicin, mesna[5]	• AD[1,2,10,11] for LMS, or if ifosfamide is not considered appropriate • Doxorubicin[1,2,6,7]	• Ifosfamide[5,7,27] • Trabectedin (for myxoid liposarcoma)[3l] • Gemcitabine and docetaxel[24,25] (category 2B)

SMAC, Lancet 1997
Slide adapted from R Ratan, M Wagner

Back to the patient

- After discussion, patient opted for neoadjuvant XRT and surgery, declined chemoRx
- Pre-surgery scan: multiple bilateral pulmonary nodules



Slide adapted from M Wagner

Overview

- Soft Tissue Sarcoma - Neoadjuvant/adjuvant therapy
- **Soft Tissue Sarcoma - Metastatic disease**
- GIST
- Bone/other

Treatment of Metastatic STS: Outline

- Doxorubicin based combinations
- Gemcitabine based combinations
- Eribulin
- Trabectedin
- Pazopanib
- Others

1970s – Doxorubicin Arrives

- Single agent *clinical* response rate of 23-35%
- RECIST response rate of 13-14% at 75 mg/m2 in recent prospective studies
- Dose Matters (45 – 60 – 75 mg/m2; 18% - 20% - 37% response rate)
- Preserving dose intensity is important
- Add cardioprotection for max. cumulative lifetime dose
- But what about combination therapy?

Historic regimens

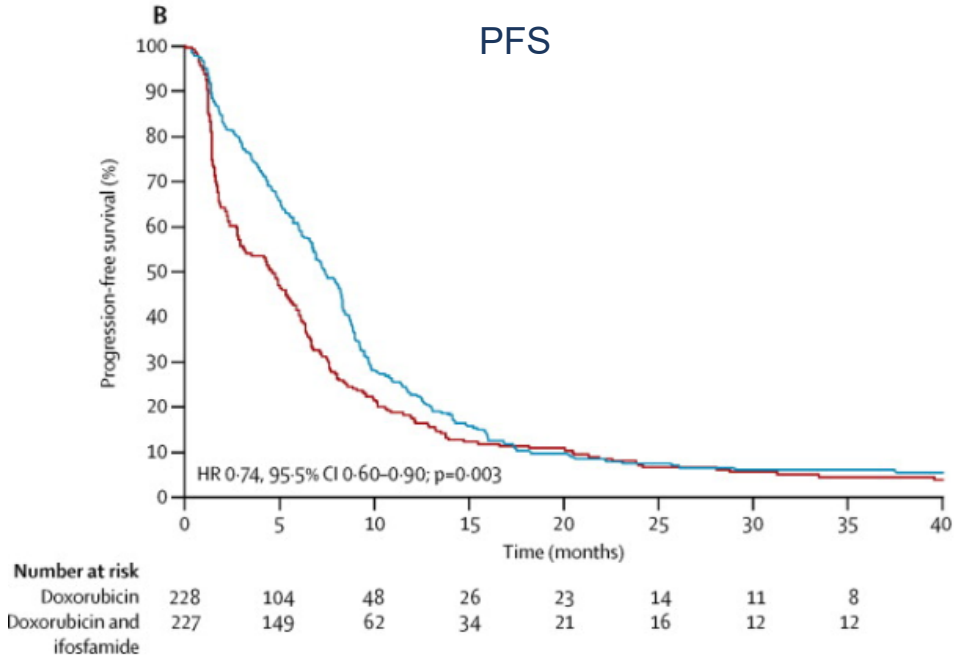
- Cy(V)ADIC- 1980s
- mAID (60mg/m2 doxorubicin, 7.5 g/m2 ifosfamide, 900 mg/m2 dacarbazine)
- Lots of toxicity with no OS benefit over less aggressive combinations and single agent Rx

Doxorubicin based combinations

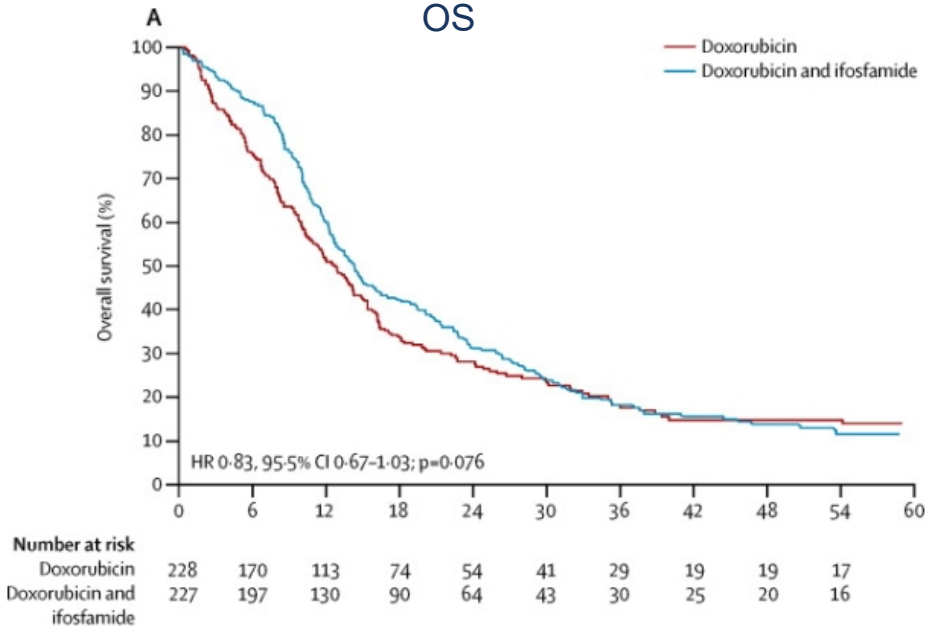
AIM (Doxorubicin 75mg/m2 + Ifosfamide 10g/m2)

- Rationale: Increase the dose of doxorubicin and ifosfamide (most active agents) after advent of growth factors
- This has been the de-facto front line combination regimen for fit patients
- Controversy about whether to use single agent versus combination therapy in metastatic, asymptomatic patients

AIM vs Doxorubicin single agent



- Median PFS: 7.4 (95%CI, 6.6-8.3) vs 4.6 (95%CI, 2.9-5.6) months
- (HR 0.72, 95%CI; 0.59-0.88, p=0.002)



- Median OS: 14.3 vs 12.8 mos
- HR 0.83 (95%CI 0.67-1.03, p=0.076)

- **Conclusion: AIM improved PFS and ORR but not OS**
- **Counterpoint: study was powered to find a 10% difference in OS, difference in study was 9%**

What are you trying to achieve with chemoRx? Palliation, life-prolongation, etc.

Judson et al, Lancet Oncology 2014

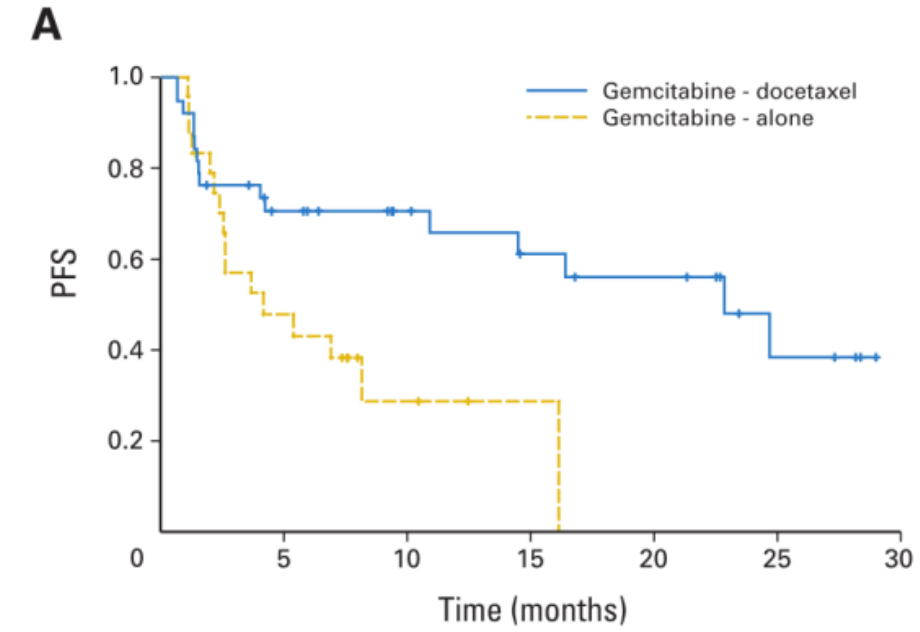
Doxorubicin based regimens: Summary

- AIM is the standard front-line regimen for ***FIT*** pts who need a response
  - Adriamycin-trabectedin for leiomyosarcoma
- ADIC is a better tolerated combination regimen for pts who can't get AIM
- Anthracycline regimens (dealer's choice) are recommended as first line therapy (Board Answer = single agent Doxorubicin okay)

	Preferred Regimens	Other Recommended Regimens	Useful in certain circumstances
First-Line Therapy Advanced/ Metastatic	**Anthracycline-based regimens:** ▸ Doxorubicin[1,2,6,7] ▸ Epirubicin[8] ▸ Liposomal doxorubicin[9] ▸ AD (doxorubicin, dacarbazine)[1,2,10,11,12] ▸ AIM[1-4,6] ▸ Ifosfamide, epirubicin, mesna[5] • Trabectedin and doxorubicin (for LMS)[13,14] • *NTRK* gene fusion-positive sarcomas only (regardless of soft tissue sarcoma subtype) ▸ Larotrectinib[h,15] ▸ Entrectinib[i,16] ▸ Repotrectinib[17]	• Gemcitabine • Gemcitabine and docetaxel[24,25] (category 2B)	• Pazopanib[k,17] (patients ineligible for IV systemic therapy or patients who are not candidates for anthracycline-based regimens) • MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[1,2,32,33] • Selpercatinib (for *RET* gene fusion-positive tumors[34]) (regardless of soft tissue sarcoma subtype) • Gemcitabine and dacarbazine[26] (category 2B)

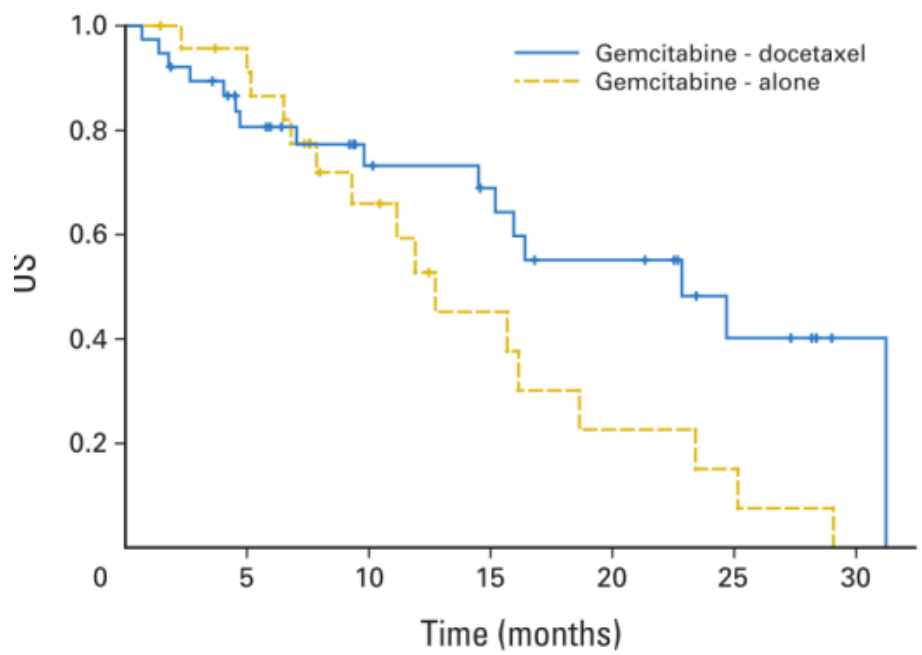
Gemcitabine vs Gemcitabine + Docetaxel

PFS



- Median PFS: 6.2 mos for gemcitabine-docetaxel and 3.0 mos for gemcitabine

OS

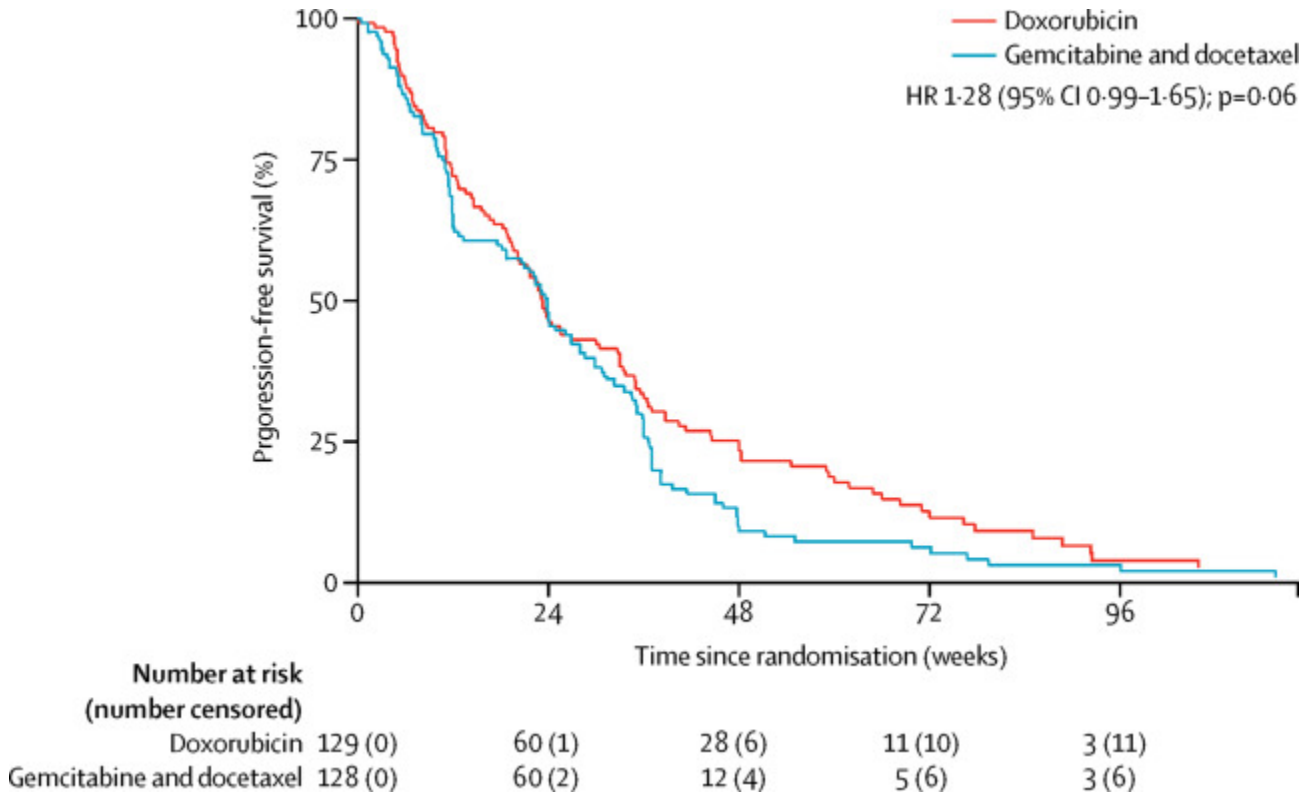


- Median OS: 17.9 mos for gemcitabine-docetaxel and 11.5 mos for gemcitabine

- **ORR: 16% (gem-docetaxel) and 8% (gem)**
- **Gem + Docetaxel improves ORR, PFS, OS over gem alone but adds more toxicity**
- **Consider single agent gemcitabine for older, less fit patients**

Maki et al, JCO, 2007

GeDDIs Trial: Gem-docetaxel vs Doxorubicin



- Gem/Tax vs single agent doxorubicin in first line chemoRx in met. STS
- Similar efficacy
- Less toxicity with doxorubicin

Maki et al, JCO, 2007

Gemcitabine based regimens: Summary

- In general, a 2nd or later line regimen, after anthracycline treatment
  - Fixed Dose Rate gemcitabine administration (10 mg/m2/min) is probably important (maximizes intracellular concentrations of the gemcitabine-triphosphate metabolite)

	Preferred Regimens	Other Recommended Regimens	Useful in certain circumstances
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Other systemic regimens for STS

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Neoadjuvant/ Adjuvant Therapy	• AIM (doxorubicin, ifosfamide, mesna)[1-4] • Ifosfamide, epirubicin, mesna[5]	• AD[1,2,10,11] for LMS, or if ifosfamide is not considered appropriate • Doxorubicin[1,2,6,7]	• Ifosfamide[5,7,27] • Trabectedin (for myxoid liposarcoma)[3l] • Gemcitabine and docetaxel[24,25] (category 2B)
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Subsequent Lines of Therapy for Advanced/ Metastatic Disease	• Anthracycline-based regimens as listed above for first-line therapy may be considered with attention to lifetime total doxorubicin dose • Pazopanib[j,k,18] • Eribulin[j,19,20] (ecommendation for category 2A for other subtypes) • Trabectedin[j,21-23] (recommendation for and category 2A for other subtypes) • Gemcitabine and docetaxel[24,25] • *NTRK* gene fusion-positive sarcomas only (regardless of soft tissue sarcoma subtype) ▸ Repotrectinib[17] (if not previously given)	• Dacarbazine[21,26] • Ifosfamide[5,7,27] • Temozolomide[j,28] • Vinorelbine[j,29] • Regorafenib[k,30] • Gemcitabine • Gemcitabine and dacarbazine[26]	• Gemcitabine and vinorelbine[35] (category 2B) • Gemcitabine and pazopanib[36] (category 2B) • Pembrolizumab[37,38] or nivolumab[j] ± ipilimumab[39-42] ▸ For myxofibrosarcoma, UPS,[f] dedifferentiated liposarcoma, cutaneous angiosarcoma, and undifferentiated sarcomas OR ▸ For TMB-H (≥10 mutations/megabase [mut/Mb])[m] regardless of soft tissue sarcoma subtype • Pembrolizumab[43] ▸ For MSI-H or dMMR tumors[n] (regardless of soft tissue sarcoma subtype) • Cabozantinib[44] (category 2B) • Afamitresgene autoleucel[45] ▸ HLA-A*02:01P, HLA-A*02:02P, HLA-A*02:03P or HLA-A*02:06P positive and whose tumor expresses the MAGE-A4 antigen (synovial sarcomas only)

Footnotes and References (SARC-G, 8 of 14)

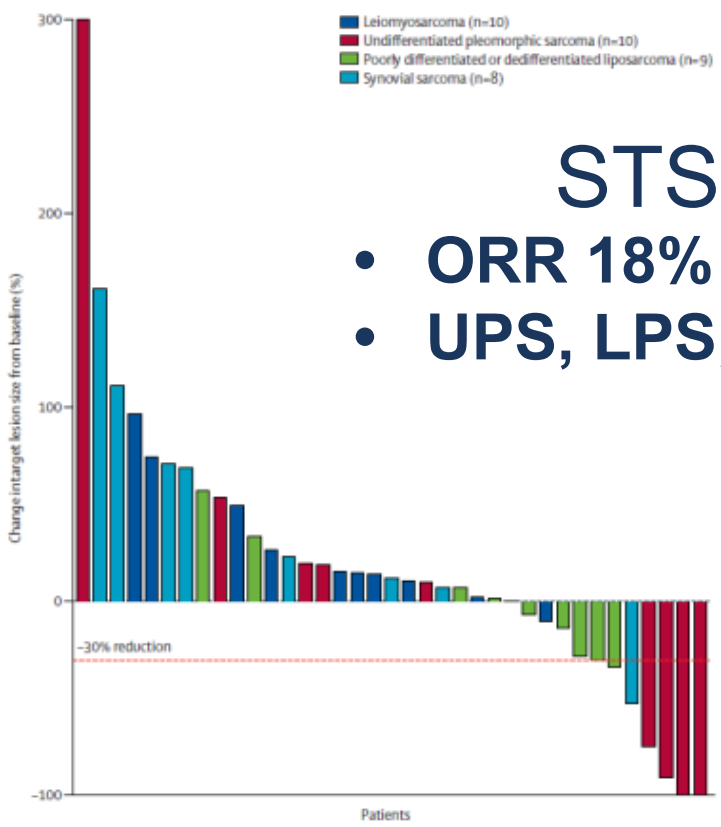
Newer Agents for STS - Highlights

- **Eribulin is FDA approved for liposarcomas (3rd line) based on improved OS but likely has activity in leiomyosarcoma as well**
- **Trabectedin is FDA approved for liposarcomas and leiomyosarcomas based on improved PFS**
  - Efficacy in translocation sarcoma (e.g. Synovial sarcoma, myxoid round cell LPS) off-label
- **Pazopanib is FDA approved for non-adipocytic soft tissue sarcomas, has modest activity (demonstrated PFS benefit)**
  - Has been studied front-line in elderly patients and shown to be non-inferior to doxorubicin

What about immunotherapy in STS?

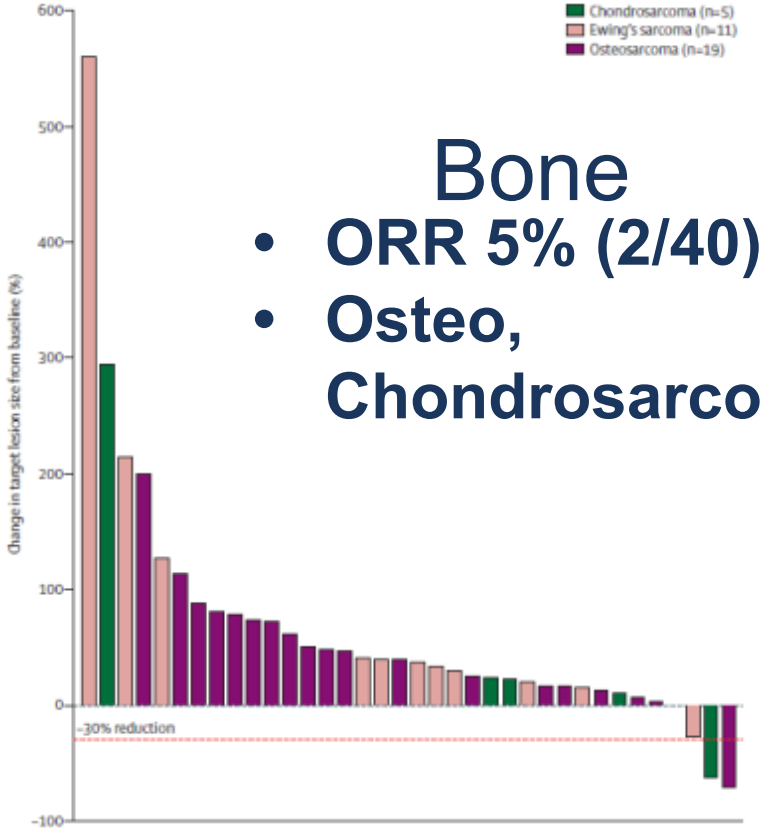
- Pembrolizumab
- Nivolumab +/- Ipilimumab
- Atezolizumab
- Afamitresgene autoleucel (Tecelra)

Activity of pembrolizumab in Sarcoma



STS

- **ORR 18% (7/40)**
- **UPS, LPS, SS**



Bone

- **ORR 5% (2/40)**
- **Osteo, Chondrosarcoma**

- **Pembrolizumab, Nivolumab +/- Ipilimumab listed in NCCN guidelines for: UPS, myxofibrosarcoma, DD LPS, cutaneous angiosarcoma**
- **But NOT FDA approved**

Tawbi et al, Lancet Oncology, 2017

Atezolizumab in Alveolar Soft Parts Sarcoma

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atezolizumab for Advanced Alveolar Soft Part Sarcoma

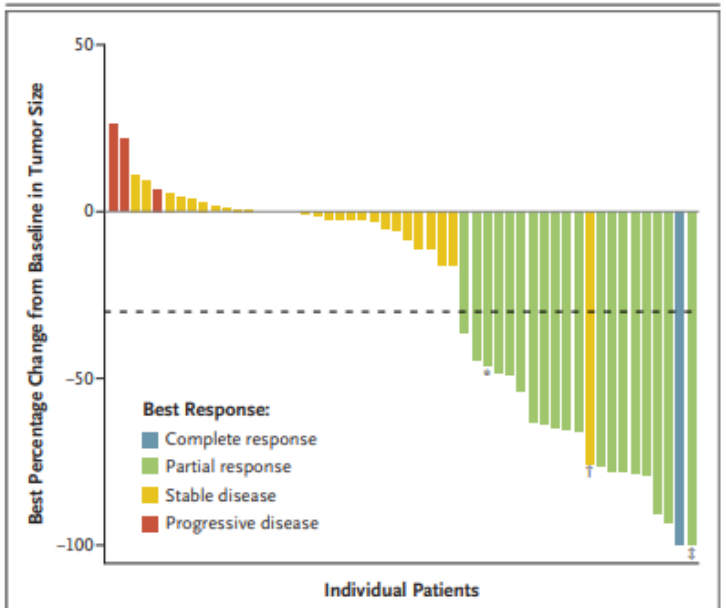


Figure 2. Best Target-Lesion Response.

The best percentage change from baseline in the target-lesion size is shown for each patient. The colors of the bars indicate the best response for each patient, and the dashed line represents a decrease of at least 30% in the target-lesion size. Patient 14 (asterisk) had an unconfirmed partial response. Patient 29 (dagger) had a partial response according to iRECIST but a best response of stable disease according to Response Evaluation Criteria in Solid Tumors, version 1.1, owing to an increase of more than 20% in target-lesion size before subsequent shrinkage (i.e., pseudoprogression). Patient 37 (double dagger) had a radiographic complete response of the target lesion, but bone abnormalities persisted.

- **ASPS: ultrarare STS, AYA**
- **ASPS-TFE3 translocation**
- **PhII single arm trial (n=52)**
- **ORR 37% (1 CR, 18 PR)**
- **PFS 20.8 mo**
- Responses occurred **regardless of baseline PD-1 or PD-L1 expression**

Atezolizumab is FDA approved for adults and children ≥2 years with unresectable or metastatic ASPS

Chen et al, NEJM, 2023

Afamitresgene autoleucel in Synovial Sarcoma

- A **genetically modified autologous T-cell therapy** targeting **MAGE-A4**, a cancer-testis antigen highly expressed in synovial sarcoma.
- Restricted to patients who are **HLA-A*02 positive** and whose tumors express **MAGE-A4** antigen
- Clinical Trial: SPEARHEAD-1 (Phase 2)
  - **Design**: Open-label, multicenter, single-arm trial
  - **Population**: 52 patients (44 with synovial sarcoma, 8 with myxoid/round cell liposarcoma)
  - **Eligibility**: Prior anthracycline/ifosfamide chemotherapy, HLA-A*02+, MAGE-A4+ tumors
  - **Treatment**: Single IV infusion following lymphodepletion (fludarabine + cyclophosphamide)
  - **ORR 39% (SS) mDOR 11.2 mo OS 2-yr survival rate (responders) 70%**
    - Cytokine release syndrome occurred in 37 (71%) of 52 of patients (one G3 event)

Afami-cel is FDA approved for adults with unresectable/metastatic synovial sarcoma, HLA-A*02+, MAGE-A4+ tumors, post-chemotherapy

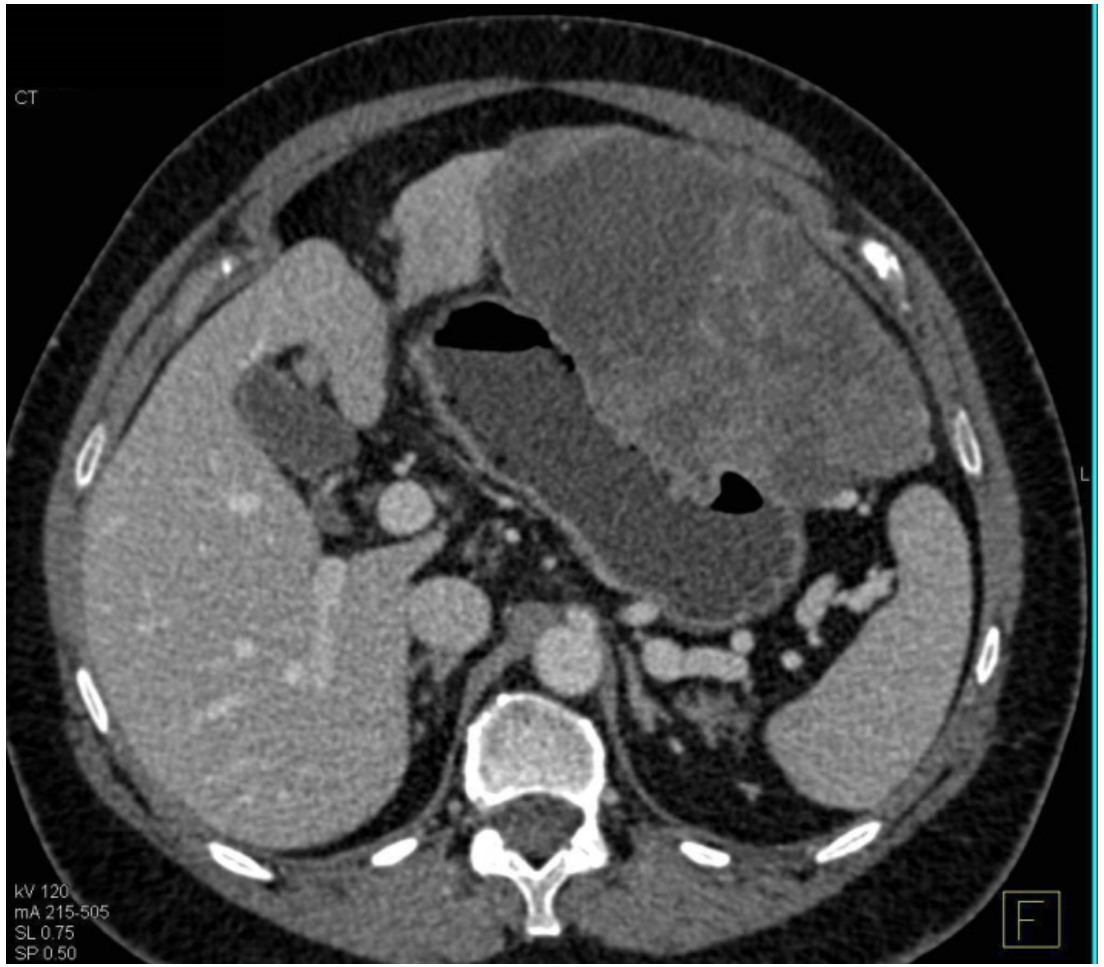
D'Angelo et al, NEJM, 2023

Overview

- STS Neoadjuvant/adjuvant therapy
- STS Metastatic disease
- **GIST**
- Bone/other

Case Presentation 2

- 50 M presents with anemia, then to ED with acute hematemesis, abdominal pain
- EGD identifies a submucosal gastric mass with ulceration



GIST Diagnosis

TABLE 1. Immunohistochemical Schema for the Differential Diagnosis of Spindle Cell Tumors of the GI Tract

	KIT (CD117)	CD34	SMA	Desmin	S-100
GIST	+	+ (60% to 70%)	+ (30% to 40%)	Very rare	5%+
Smooth muscle tumor	−	+ (10% to 15%)	+	+	Rare
Schwannoma	−	+ (usually Antoni B)	−	−	+
Fibromatosis	Disputed*	Rare	+	Rare cells	−

Abbreviation: SMA, smooth muscle actin.
*Most, but not all authors report that fibromatoses are negative for KIT.

- Another GIST marker is DOG1 (a calcium channel seen on GIST cells)
  - DOG1 staining is by IHC and helps establish the diagnosis
- + KIT expression (IHC) ≠ + KIT mutation (PCR, NGS)

Fletcher et al, Human Path 2002

Medical Management: Targeting GIST Biology

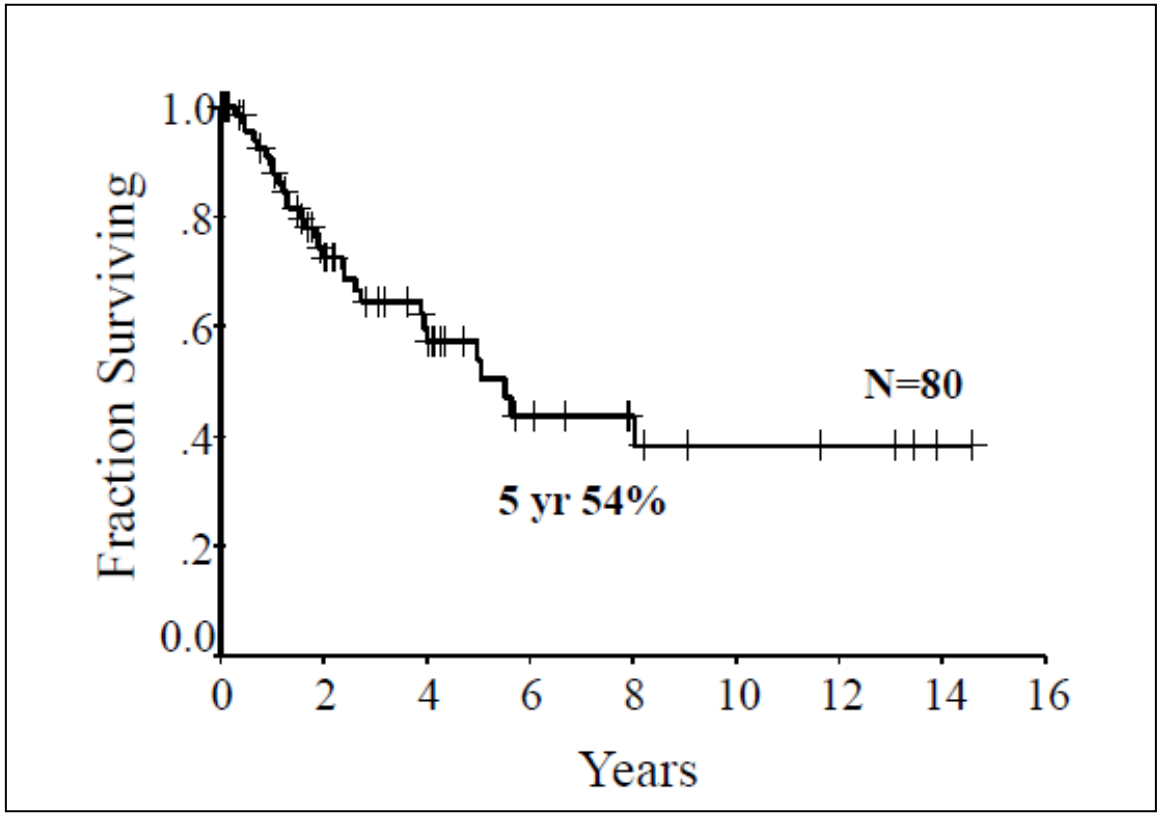
- Mutations in GIST- *these are different from IHC and can only be detected by PCR or other sequencing based methods*
  - KIT (~80%)- *NOTE: KIT expression by IHC is not the same as having a KIT mutation*
    - *Exon 11- most common, 400 mg imatinib*
    - *Exon 9- often in small bowel, 800 mg imatinib*
  - PDGFR (~10%)- most mutations responsive to imatinib
    - Exon 18 mutations, **D842V**- use avapritinib
  - "WT"- 85% of GISTs in children and 10% in adults
    - SDH
    - BRAF
    - NF1
    - NTRK fusion
    - Other…

GIST Treatment

- Surgery
- Medicines
  - Tyrosine kinase inhibitors (TKIs)
  - Can be given before surgery if needed→ takes a long time (many months) before enough tumor shrinkage to get to surgery
- Rarely radiation
- Radiofrequency ablation (RFA), embolization, or chemoembolization (liver mets)

Historic Surgical Outcomes

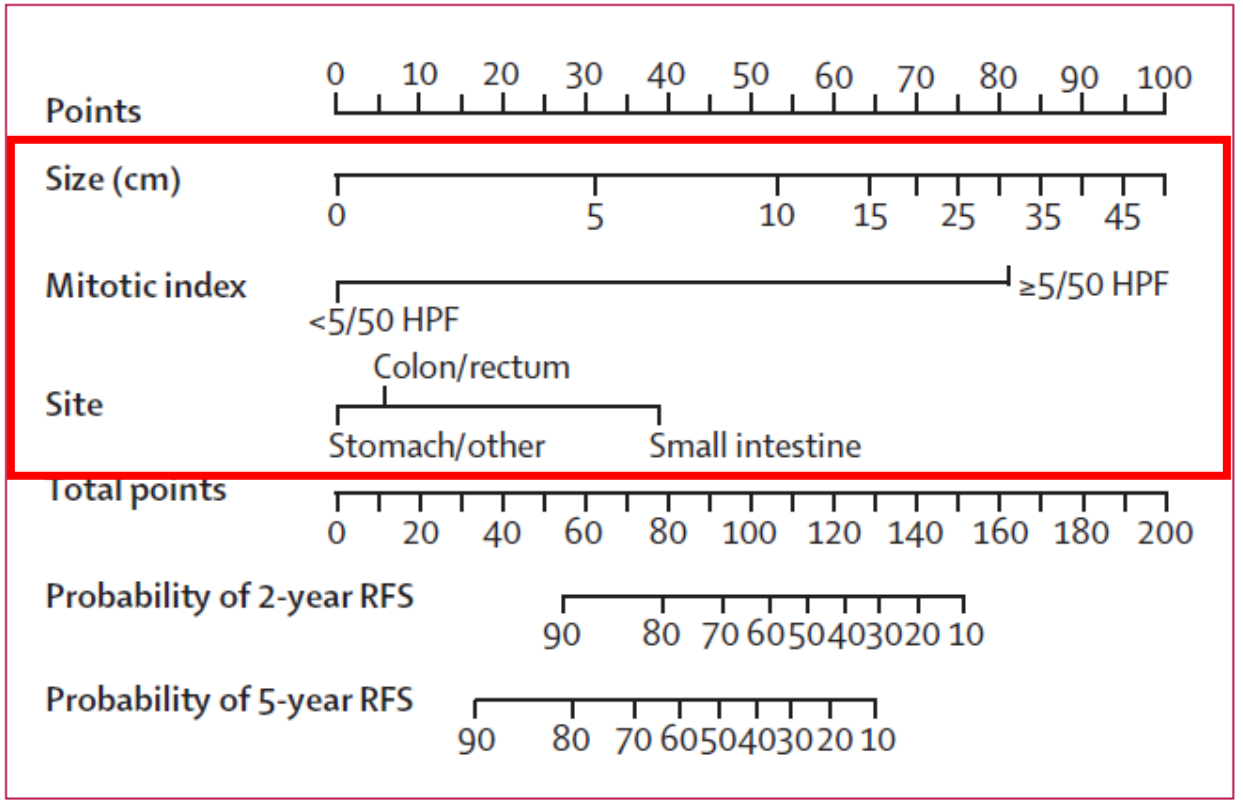
- 50% of patients can recur postoperatively, usually in the liver or peritoneum, and will die within 5 years **without additional treatment**



DeMatteo, *Ann Surg,* 2000.

Predicting Postop Recurrence

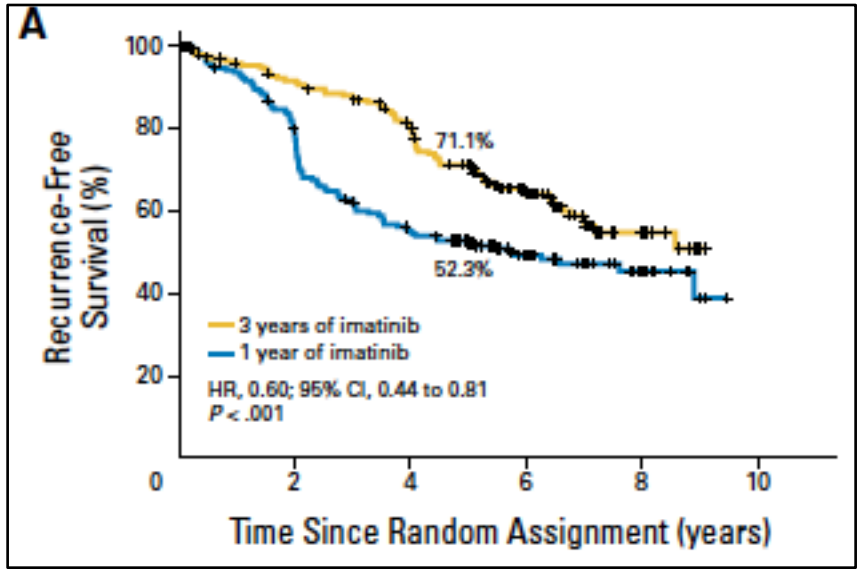
- **Who needs adjuvant TKI after surgery?**

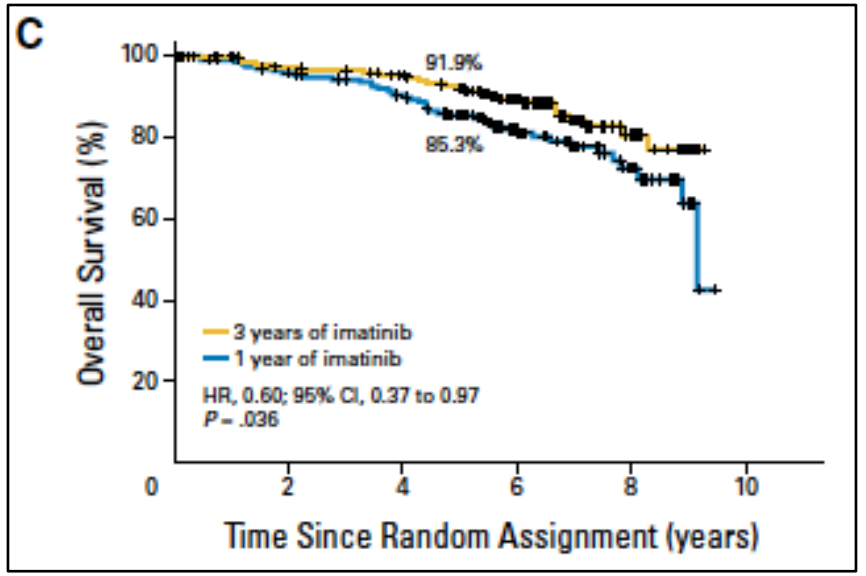


Gold et al. Lancet Oncol 2009; MSKCC GIST Nomogram

Medical Management: GIST Adjuvant Rx

- Adjuvant imatinib for high risk patients, 3 years tx





Improved RFS HR 0.60, p<0.001

Improved OS HR 0.60, p<0.036

- Adjuvant imatinib 3y vs 1y improved RFS 20%, OS < 10% (SSGXVIII/AIO trial)

Joensuu, *J Clin Onc,* 2014.

Adjuvant imatinib Therapy for GIST

- **At least 3 years of treatment after surgery for a high-risk GIST is considered standard of care (FDA approved duration)**

- **In the adjuvant setting the optimal treatment duration with imatinib is not known**
  - IMADGIST trial: 6 yrs > 3 yrs for highest risk pts

- **Many GIST experts believe that longer treatment is even better and will continue patients for as long as they are tolerating the drug and there is no tumor recurrence**
    - **Can be lifelong, but often length of treatment beyond 3 years is a discussion with the patient of risks vs potential benefit**

Medical Management: GIST Metastatic Disease

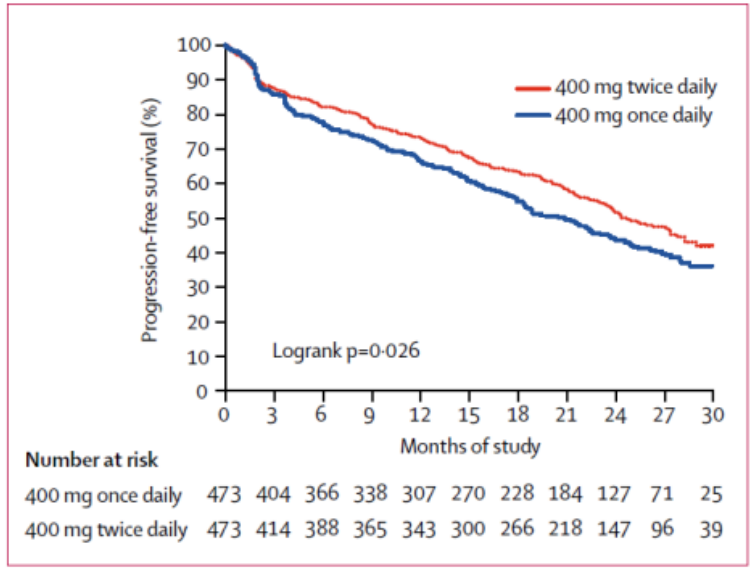
- **Imatinib (or Avapritinib if insensitive PDGFRA exon 18 mutation) → Sunitinib* → Regorafenib* → Ripretinib* → Clinical Trial**

*** Always consider a clinical trial enrollment**

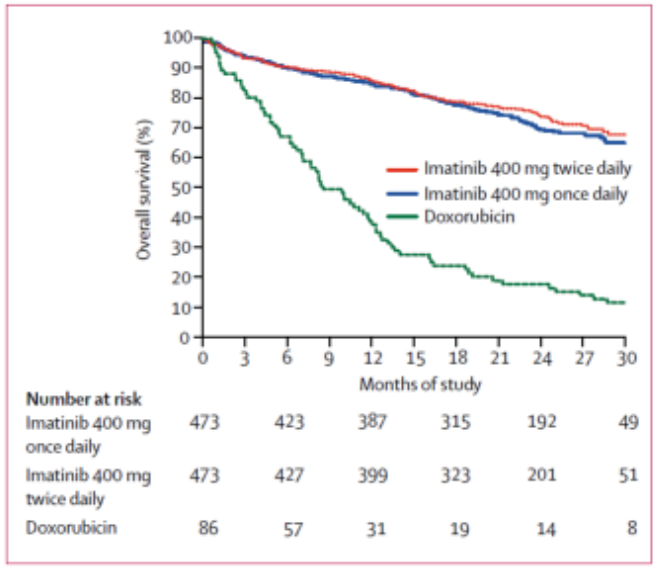
Medical Management: Metastatic GIST

- **1st line: imatinib (EORTC, SWOG S0033, MetaGIST)**

1°: Progression-free Survival



2°: Overall Survival

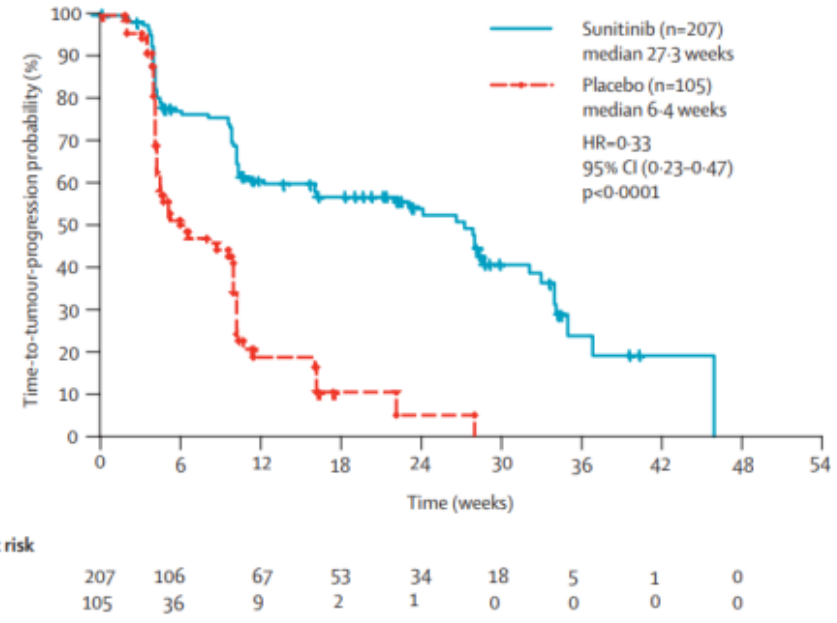


Median PFS 19.5 – 33 mo; Median OS 46.8-68 mo

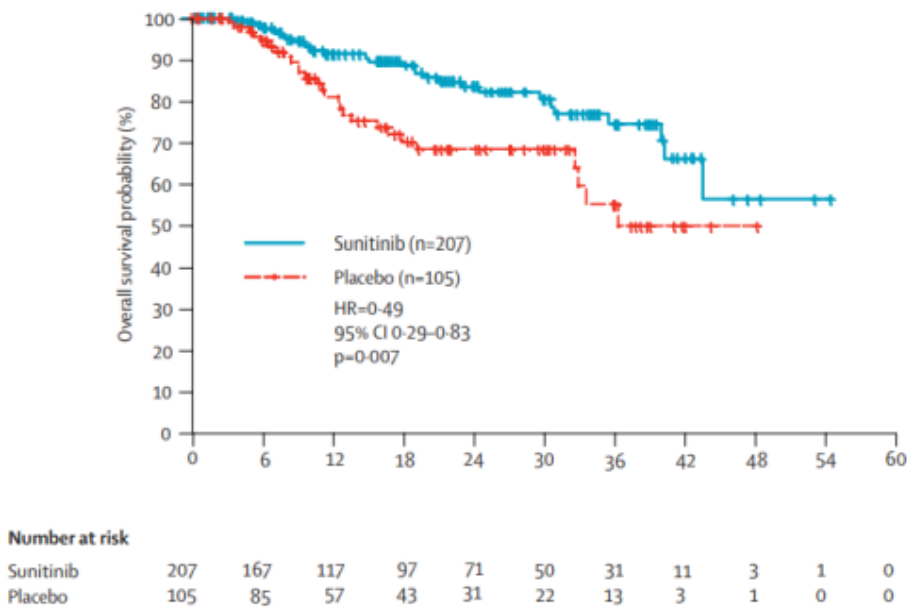
Verweij *et al.* Lancet 2004, 364. 1127-34.

Medical Management: 2nd Line Metastatic GIST

- **2nd line: sunitinib** (Demetri 2006)



Improved Progression Free Survival

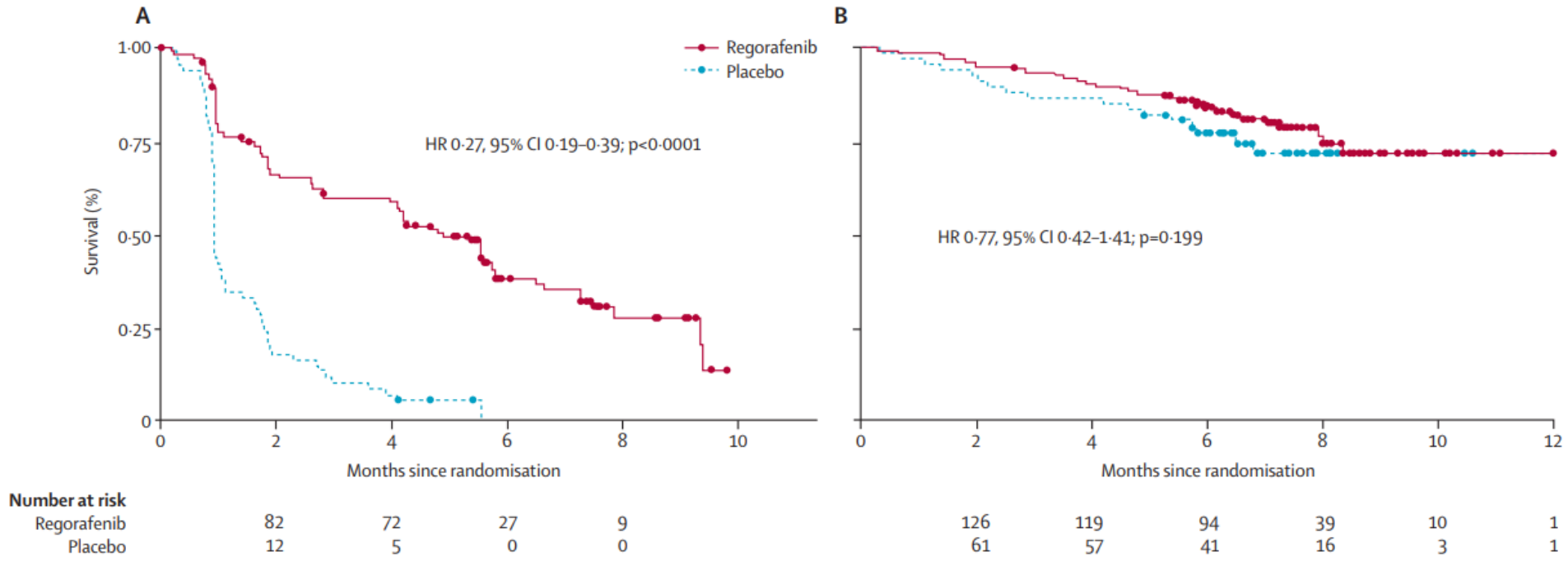


Improved Overall Survival

- **Median PFS on sunitinib was 27 weeks (about 7 months)**

Medical Management: 3rd Line Metastatic GIST

- **3rd line: Regorafenib** (Demetri 2013)



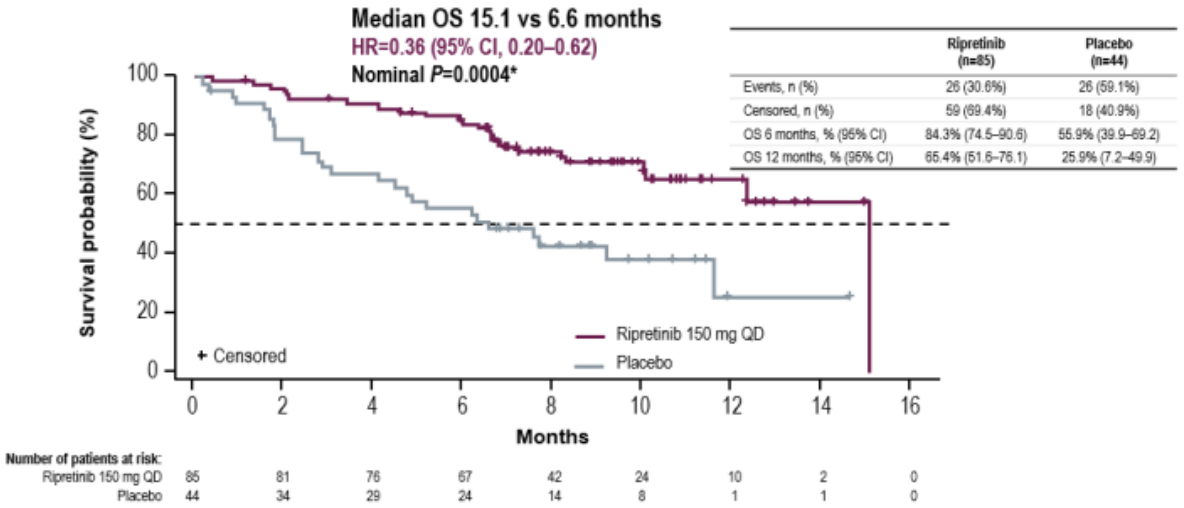
Improved Progression Free Survival
4.8 mo > 0.9 mo

Trend Improved Overall Survival

Medical Management: 4th Line Metastatic GIST

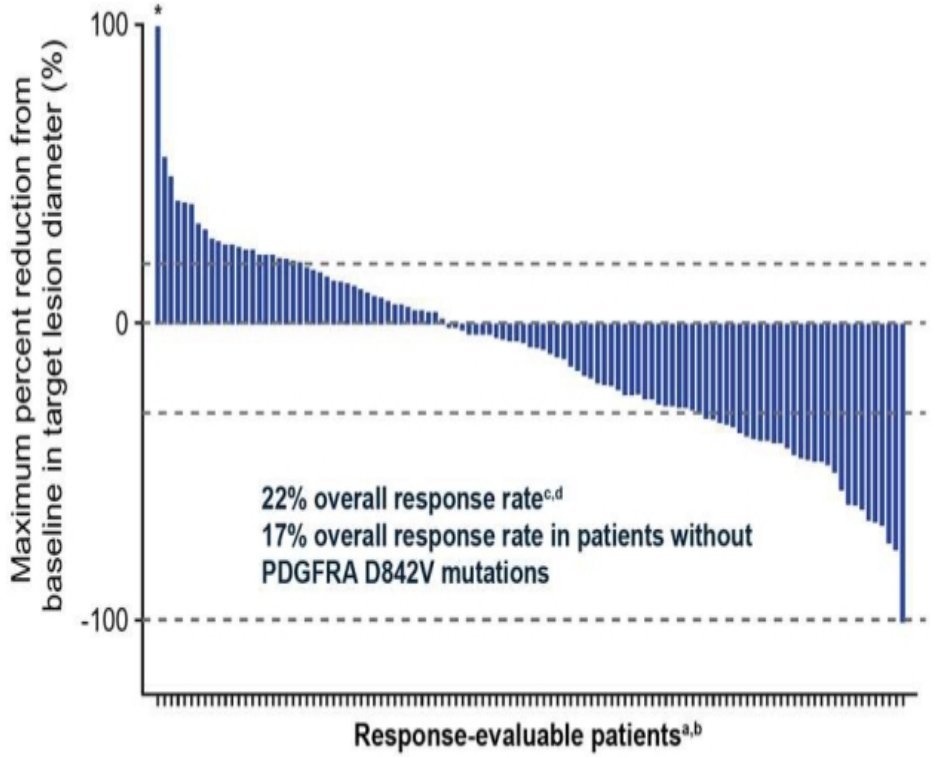
- **4th Line and beyond: Ripretinib**

Ripretinib



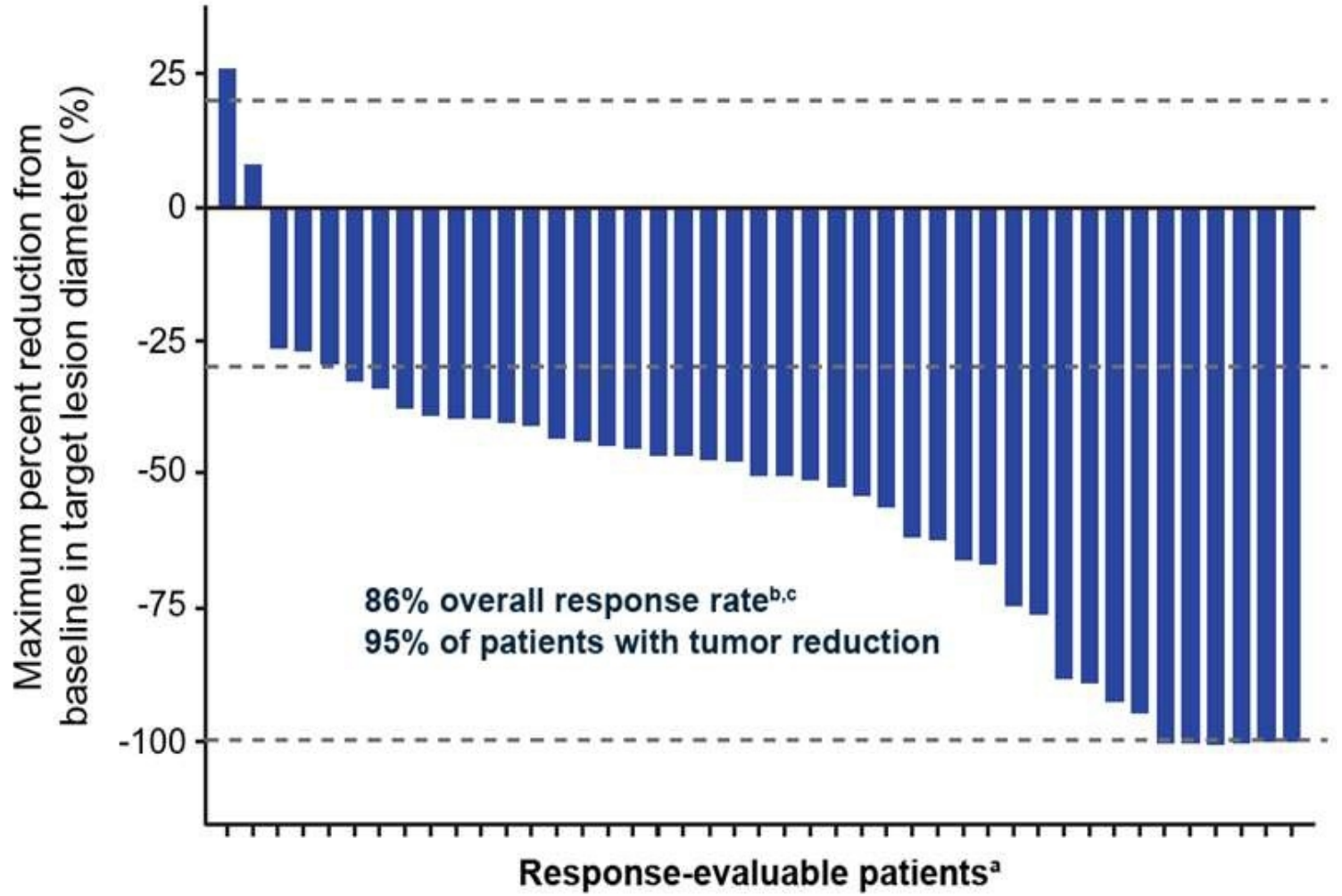
	Ripretinib (n=85)	Placebo (n=44)
Events, n (%)	26 (30.6%)	26 (59.1%)
Censored, n (%)	59 (69.4%)	18 (40.9%)
OS 6 months, % (95% CI)	84.3% (74.5–90.6)	55.9% (39.9–69.2)
OS 12 months, % (95% CI)	65.4% (51.6–76.1)	25.9% (7.2–49.9)

Avapritinib



Blay *et al.* Lancet 2020; George et al, Oncologist 2021

Medical Management: Metastatic GIST



- **Avapritinib in PDGFRA exon 18 mutant GIST**

Heinreich et al, Lancet Oncology 2020

GIST Summary

- Most cases have KIT or PDGRA mutations

- Localized disease
  - Surgery +/- adjuvant imatinib based on risk stratification

- Metastatic disease
  - KIT/PDGFR mutation testing (sequencing)
  - 1st choice usually Imatinib 400 mg daily
  - Sunitinib, Regorafenib, Ripretinib
  - Avapritinib for PDGFRa D842V mutation
  - No role for standard chemotherapy

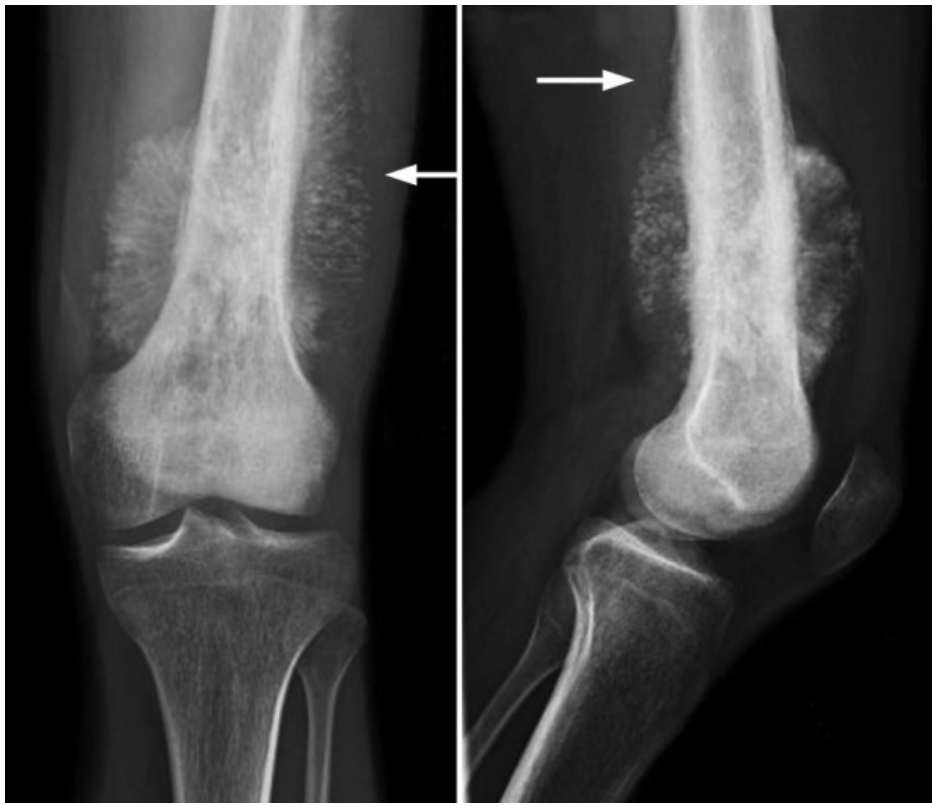
Overview

- STS Neoadjuvant/adjuvant therapy
- STS Metastatic disease
- GIST
- **Bone/other**

Case Presentation 3

- 20 M with R leg knee pain, swelling
- X-RAY shows:
  - Lytic and sclerotic lesion
  - Aggressive periosteal reaction
    - “Sunburst appearance”
  - Soft tissue mass w Calcification

Dx: Osteosarcoma



Osteosarcoma = Metaphysis of long bones (e.g. distal femur, prox tibia, prox humerus)

Ewing Sarcoma = Diaphysis of long bones (shaft of long bones), pelvis, rib

Orthoinfo.aaos.org

Medical Management: Bone/Pediatric Sarcomas

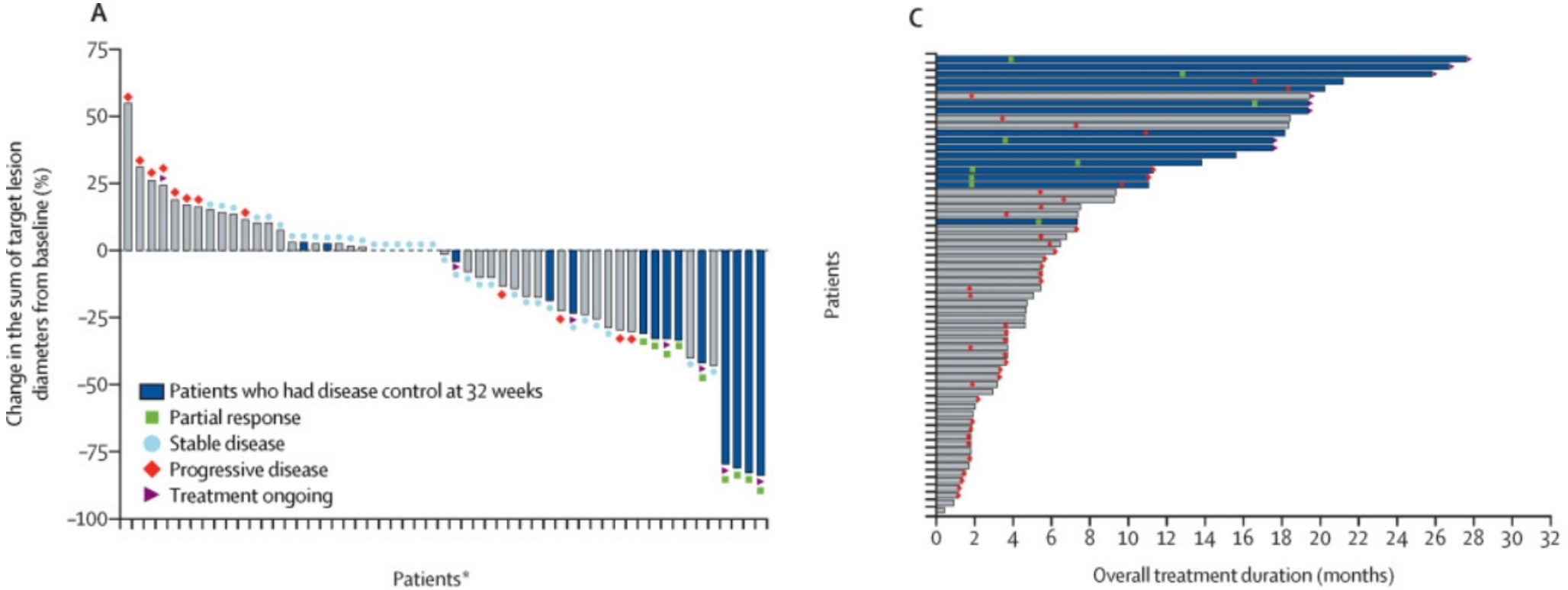
- Osteosarcoma
  - MAP-surgery-MAP (do not tailor adjuvant based on % necrosis)
- Ewing sarcoma
  - (q2 week) ddVDC/IE – XRT/surgery – ddVDC/IE
- Rhabdomyosarcoma
  - Alveolar/Embryonal/spindle cell/sclerosing subtypes
  - Risk stratification, ALL REQUIRE MULTI-AGENT CHEMOTHERAPY
- Chondrosarcoma (conventional) - Surgery if possible, not very responsive to chemo
- Giant Cell Tumor of Bone- denosumab

Special Other Histologies (simply recognizing the disease entity is a possible boards question)

- Angiosarcoma- responsive to taxanes
- Dermatofibrosarcoma Protuberans (DFSP)- imatinib
- PVNS- Pexidartinib (CSF1R inhibition)
- Desmoid tumor- sorafenib, nirogacestat (associated with FAP)
- Inflammatory myofibroblastic tumor (IMT)- if ALK positive, can respond to ALK inhibitors
- PEComa- mTOR inhibitors (nab-sirolimus)
- **Pediatric sarcomas in adults - aggressive multiD care**

Special Other Histologies: Epithelioid sarcoma

- **Epithelioid sarcoma frequently has loss of** INI1/*SMARCB1*



- **Median PFS 5.5 months, ORR 14.5%**
- **Tazemetostat FDA approved for epithelioid sarcoma**

Gounder et al, Lancet Onc 2020

Fred Hutch Cancer Center

Thank you

UW Medicine