Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Oncology Board Review: Sarcoma

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Disclosures

- Advisory: Tempus, Deciphera, Adaptimmune
- Grants/Research to institution: Athenex, Deciphera, Incyte, Adaptimmune, GSK, Inhibrx

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

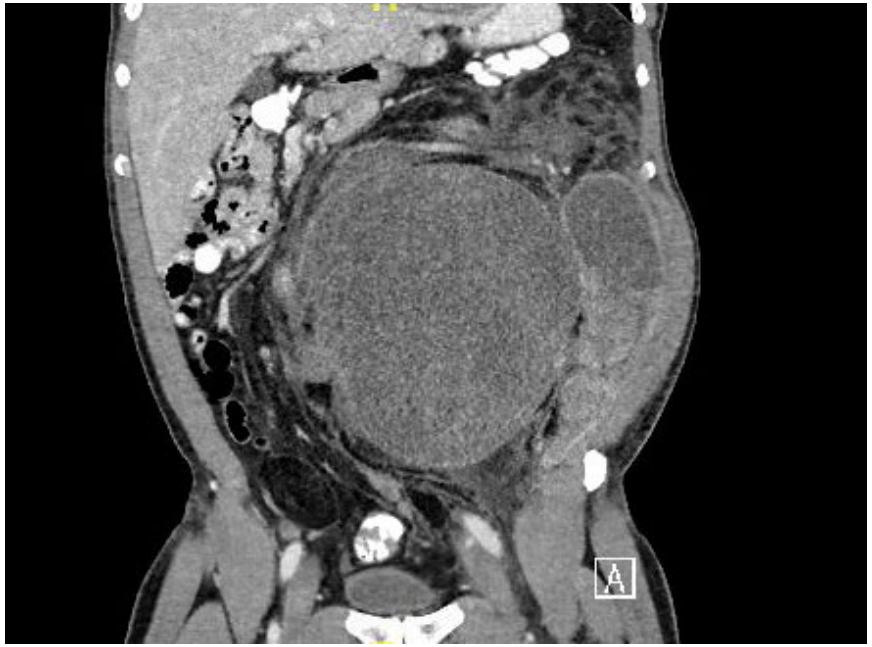
Overview

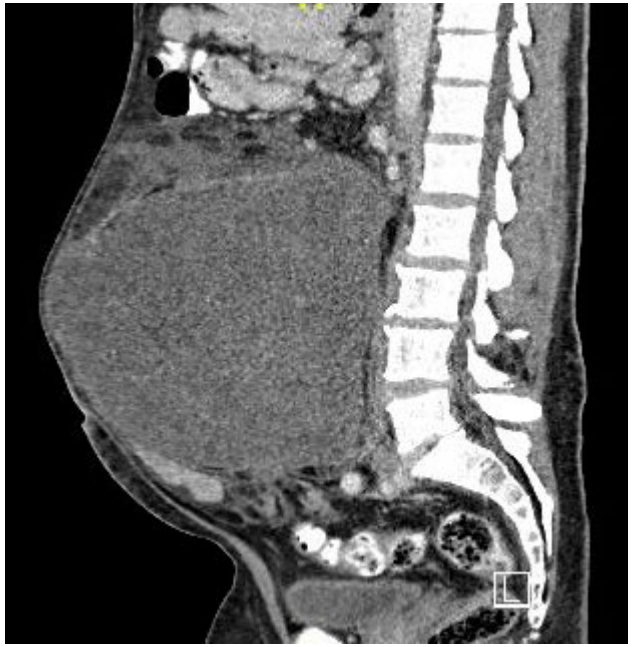
- STS Neoadjuvant/adjuvant therapy
- STS Metastatic disease
- GIST
- Bone/other

Case Presentation

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

Case Presentation





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

Overview

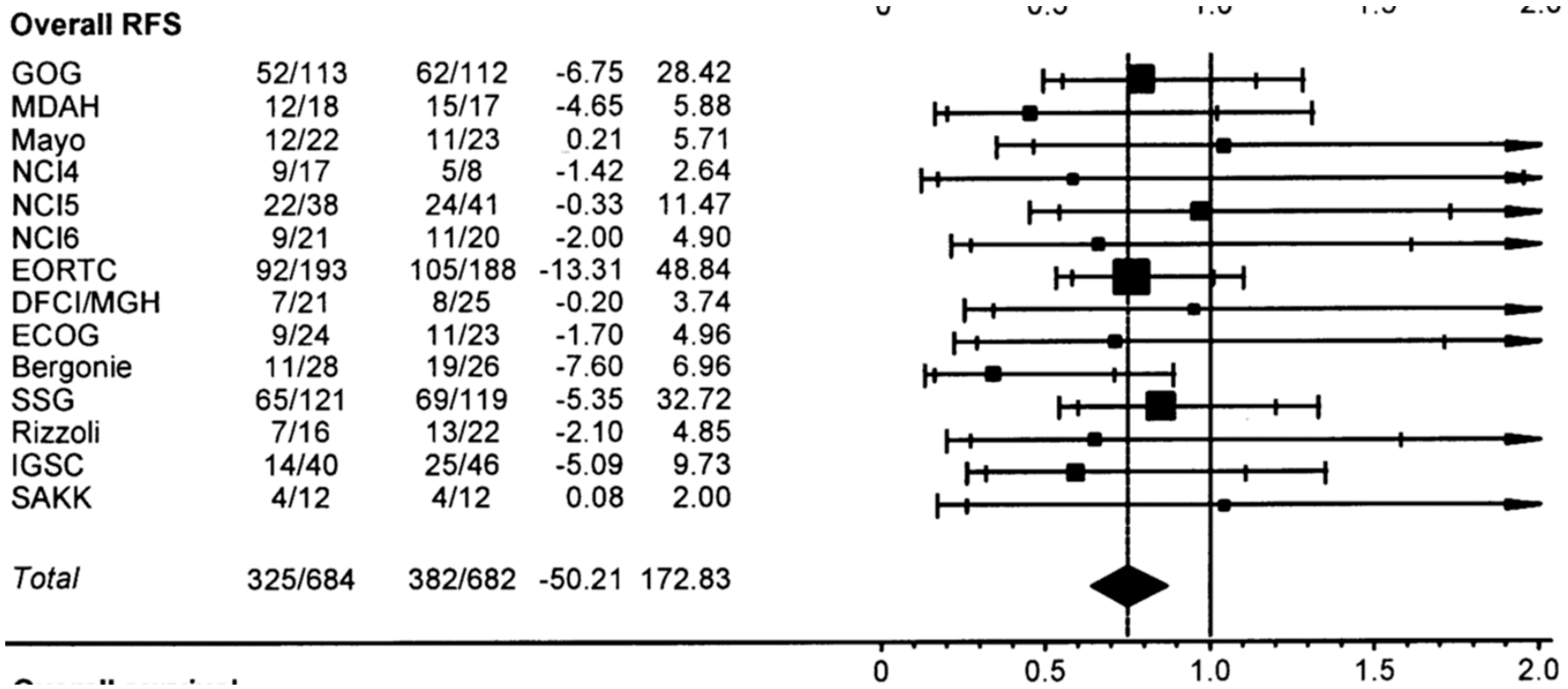
- **STS Neoadjuvant/adjuvant therapy**
- **STS Metastatic disease**
- **GIST**
- **Bone/other**

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
- Most extremity STS need XRT for local control
- Less clear for RP and abdominal sarcomas
  - Usually a case by case assessment- newer data arguing against RT in RP sarcomas

Slide adapted from R. Ratan

Adjuvant chemotherapy

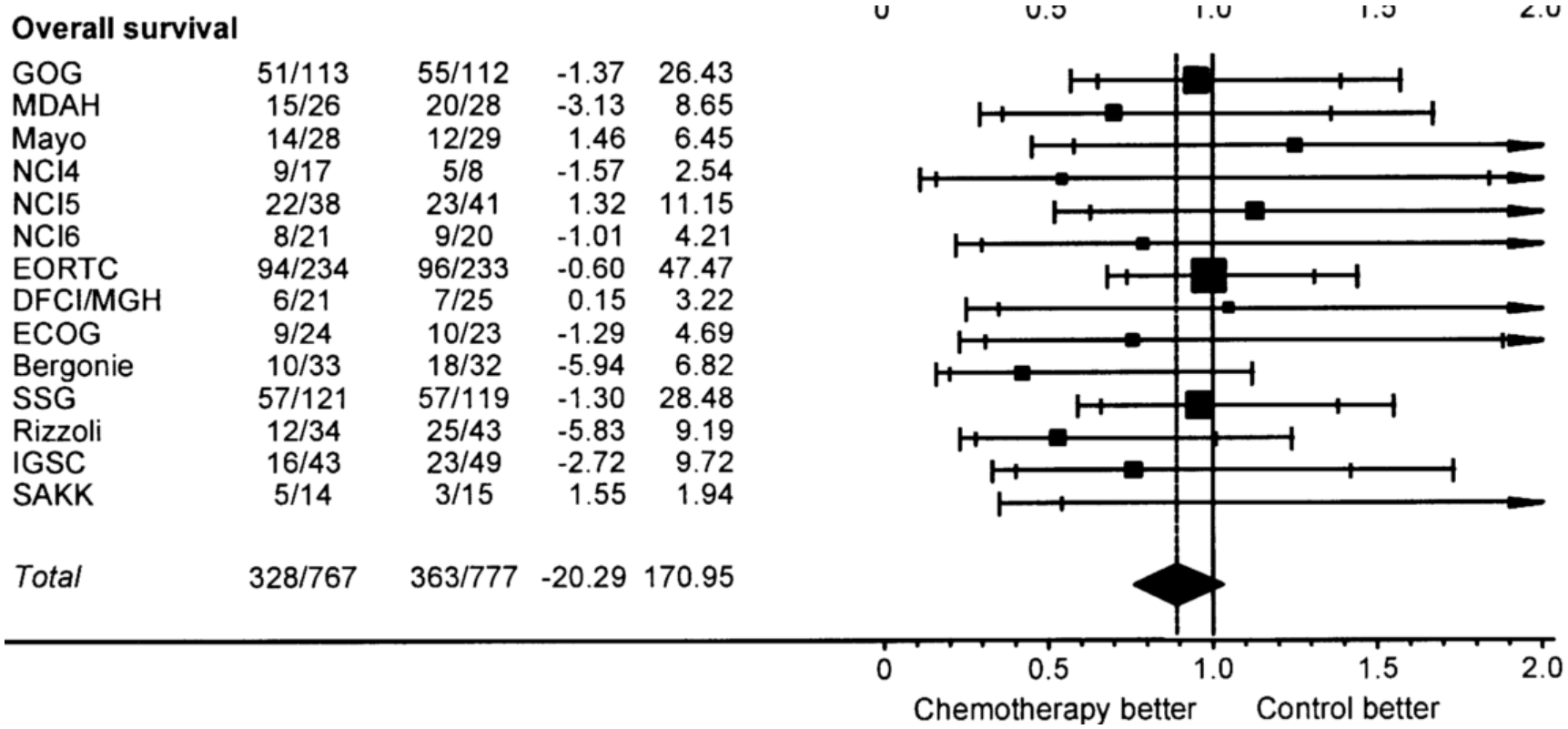


- **Improvement in RFS**

SMAC, Lancet 1997

Adjuvant chemotherapy

Overall survival				
GOG	51/113	55/112	-1.37	26.43
MDAH	15/26	20/28	-3.13	8.65
Mayo	14/28	12/29	1.46	6.45
NCI4	9/17	5/8	-1.57	2.54
NCI5	22/38	23/41	1.32	11.15
NCI6	8/21	9/20	-1.01	4.21
EORTC	94/234	96/233	-0.60	47.47
DFCI/MGH	6/21	7/25	0.15	3.22
ECOG	9/24	10/23	-1.29	4.69
Bergonie	10/33	18/32	-5.94	6.82
SSG	57/121	57/119	-1.30	28.48
Rizzoli	12/34	25/43	-5.83	9.19
IGSC	16/43	23/49	-2.72	9.72
SAKK	5/14	3/15	1.55	1.94
Total	328/767	363/777	-20.29	170.95



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

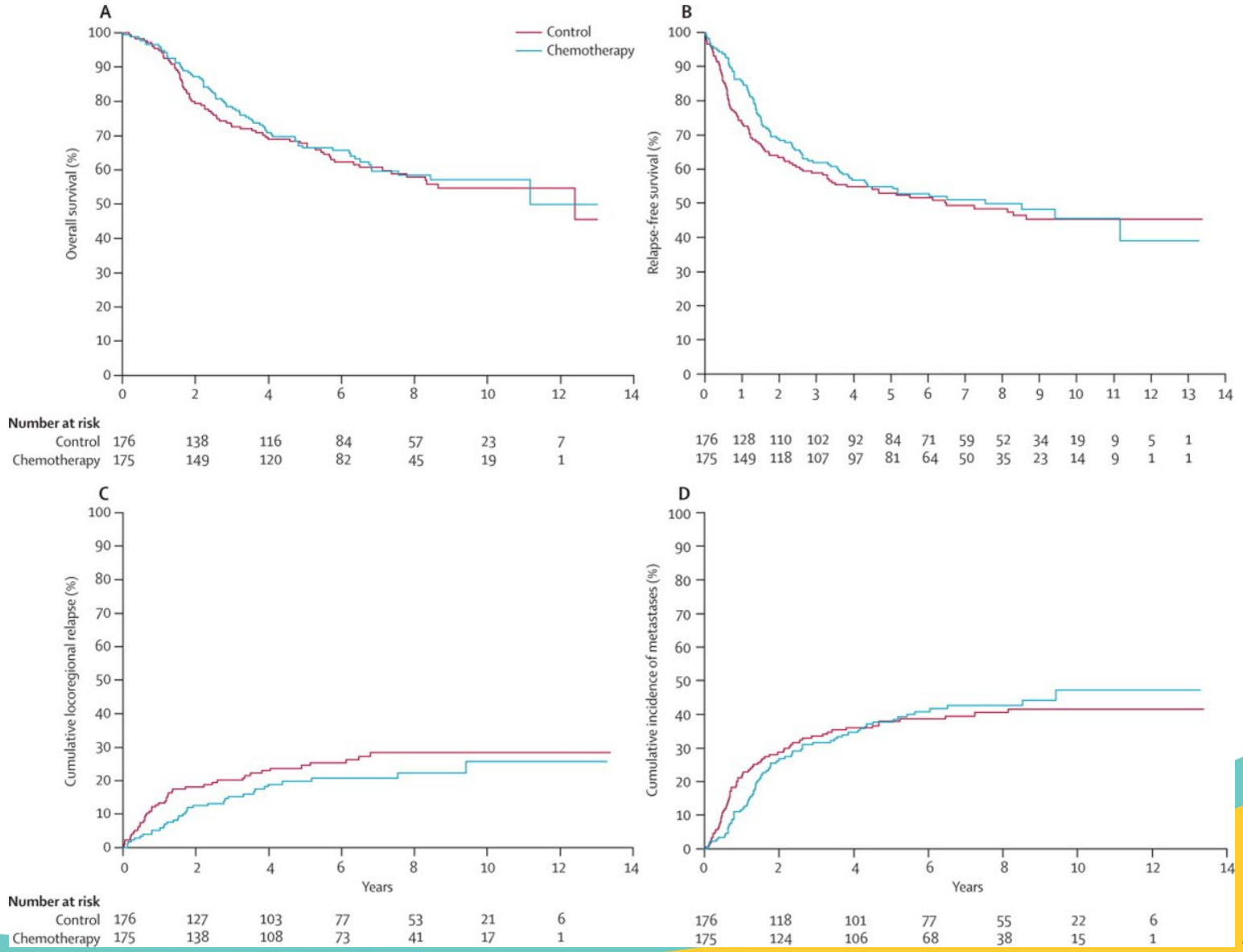
SMAC, Lancet 1997

Adjuvant chemotherapy: EORTC study

- Randomized
- Doxo 75+Ifos 5
  Vs no chemo

- All pts had surgery and RT as per SOC

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



Woll et al, Lancet Onc 2012

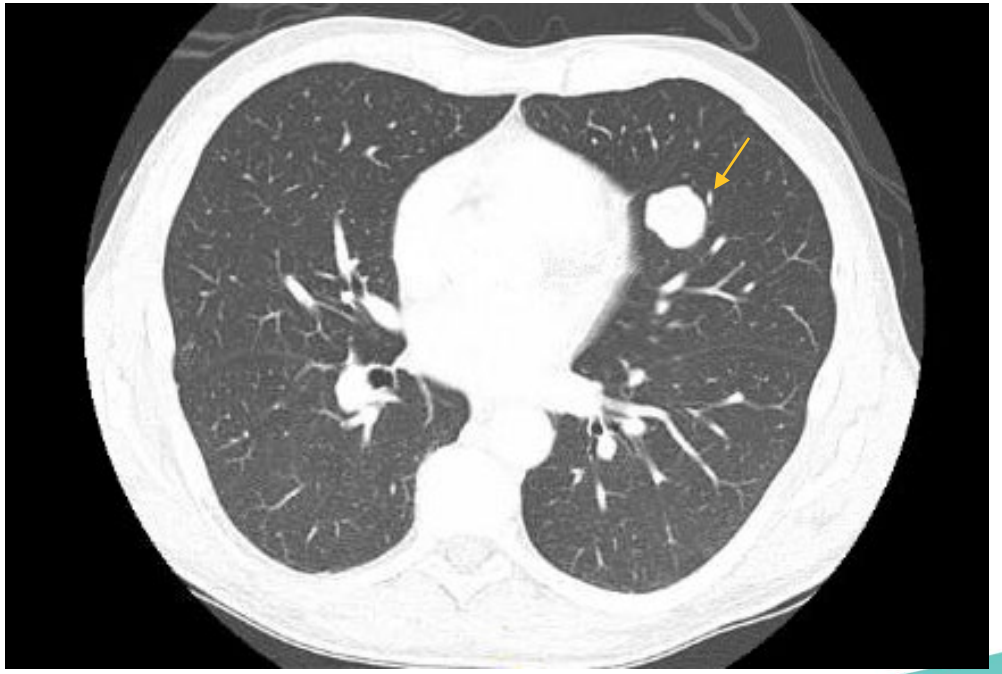
Adjuvant chemotherapy: summary of sarcoma metanalysis consortium

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

SMAC, Lancet 1997
Slide adapted from R. Ratan

Back to the patient

- After discussion, patient opted for neoadjuvant XRT and surgery, he did not want chemo
- Pre-surgery scan: multiple bilateral pulmonary nodules



Overview

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

Treatment of Metastatic STS: Outline

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

Historic regimens

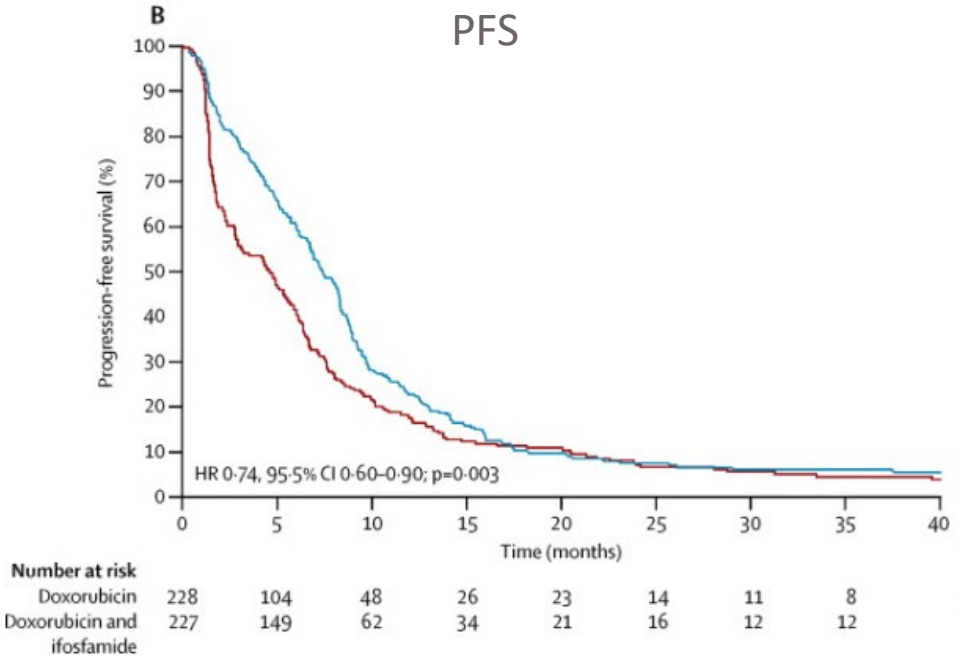
- Cy(V)ADIC- 1980s
- mAID (60mg/m2 doxorubicin, 7.5 g/m2 ifosfamide, 900 mg/m2 dacarbazine)
- Lots of toxicity with no OS benefit over less aggressive combinations and single agent

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

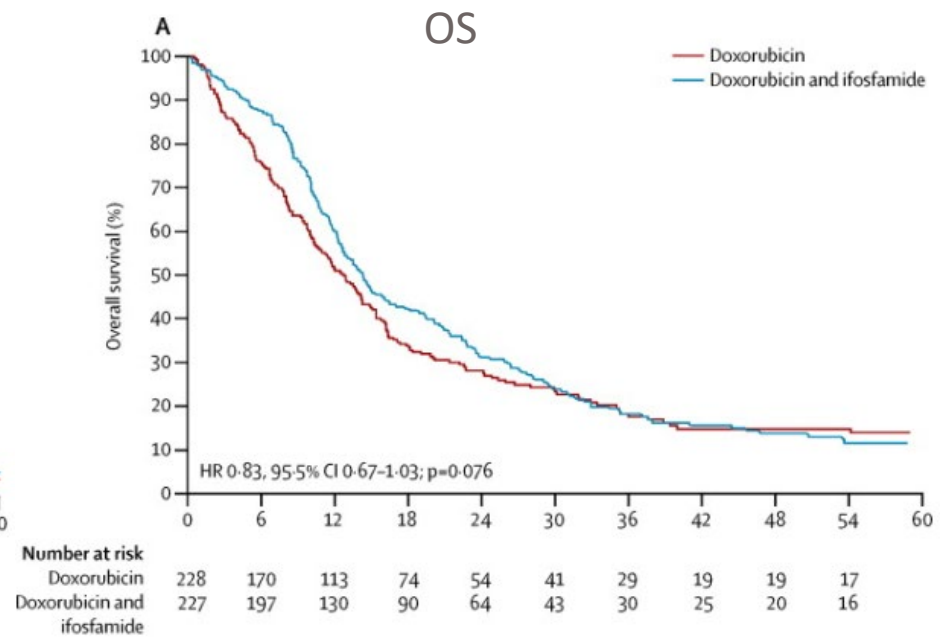
AIM vs Doxorubicin single agent

PFS



- 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)

OS

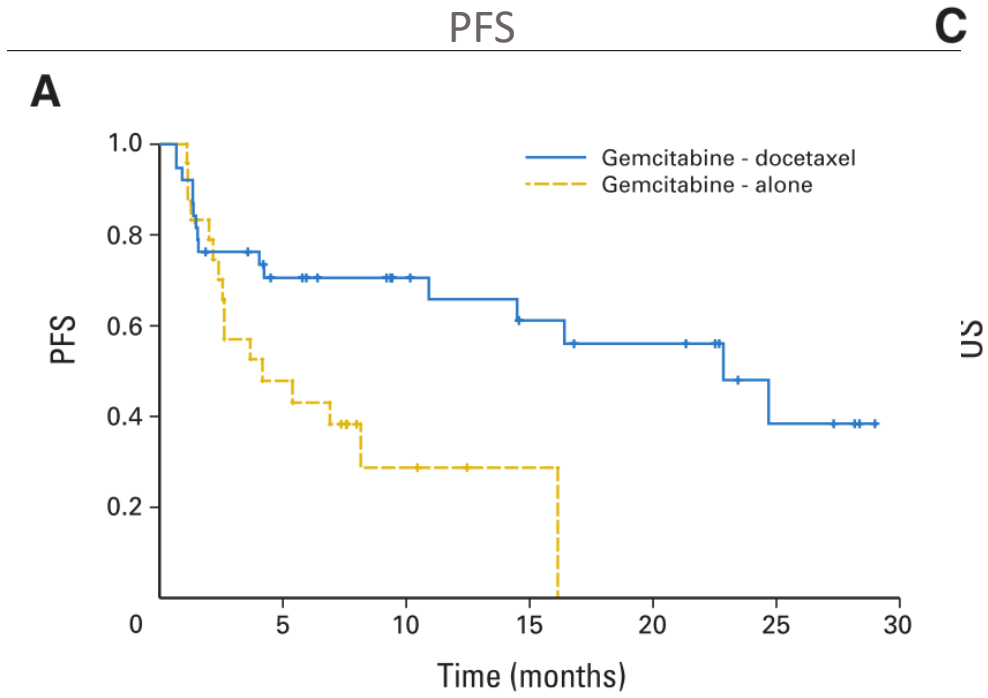


- Median OS: 14.3 vs 12.8 mos
- HR 0.83 (95%CI 0.67-1.03, p=0.076)

- **Conclusion: AIM improved PFS and ORR but not OS, single agent doxo is SOC 1st line for metastatic STS**
- **Doxorubicin lifetime use limited by cardiotoxicity risk**

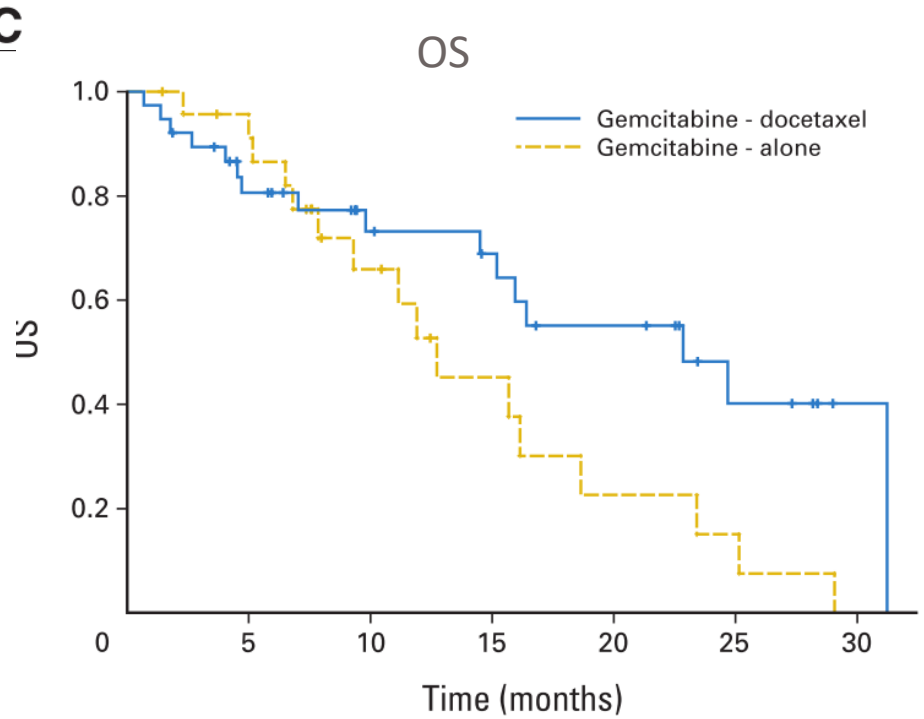
Judson et al, Lancet Oncology 2014

Gemcitabine vs Gemcitabine + Docetaxel



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

- **ORR: 16% (gem-docetaxel) and 8% (gem)**

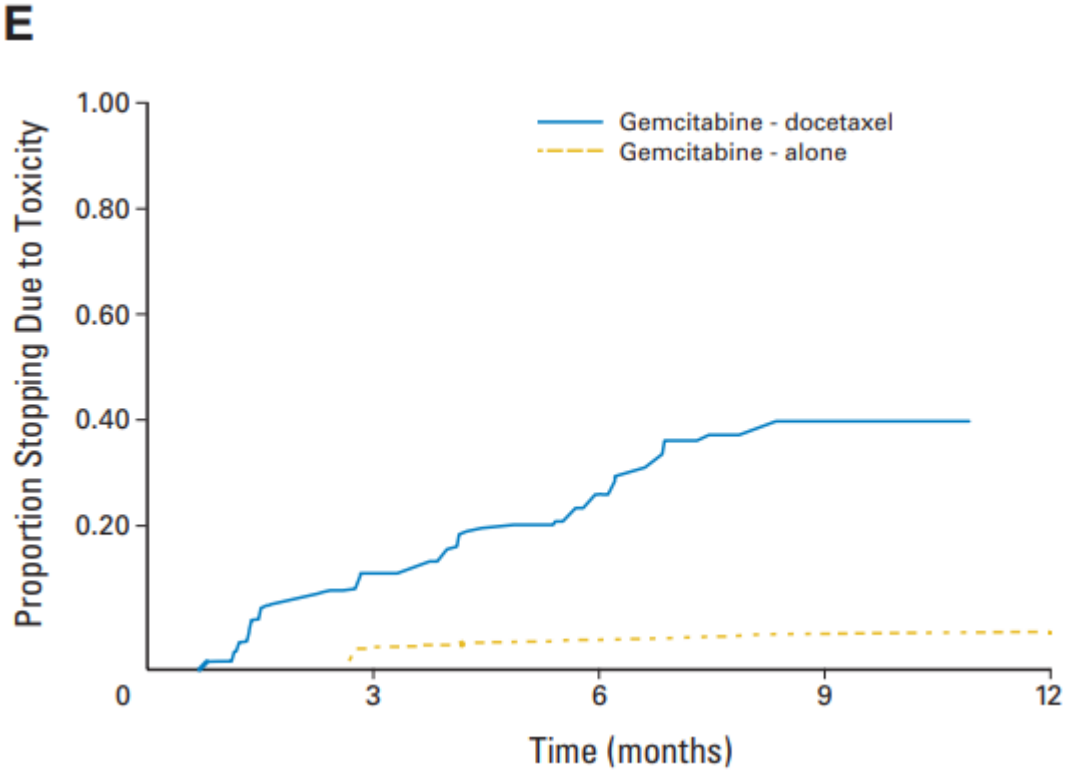


- Median OS: 17.9 mos for gemcitabine-docetaxel and 11.5 mos for gemcitabine

Maki et al, JCO, 2007

Gemcitabine vs Gemcitabine + Docetaxel

- Additional toxicity with docetaxel



- Conclusion: Gem-Tax improves PFS and OS over gem alone but with extra toxicity

Maki et al, JCO, 2007

Gemcitabine

- Gemcitabine + Dacarbazine

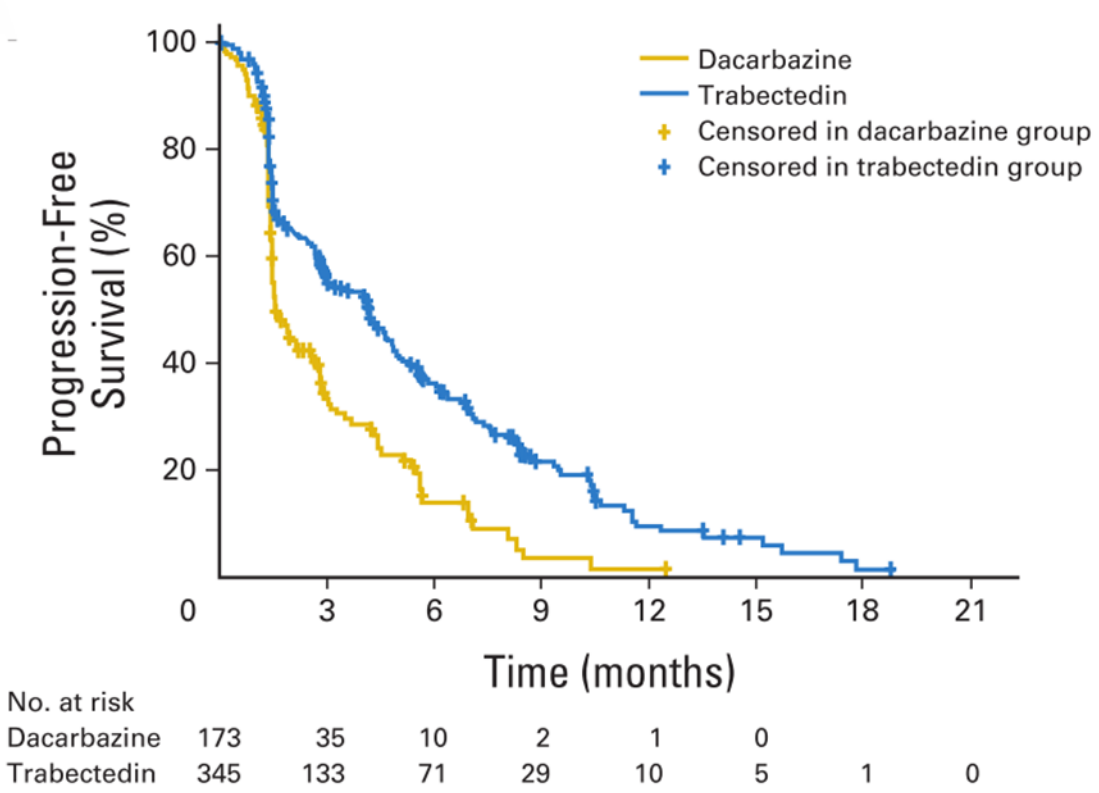
- Single Agent Gemcitabine, especially for older adults or those unable to tolerate the combinations

Trabectedin

- Compound isolated from sea squirt
- Binds DNA minor groove
- Initial studies showed it has activity in “L-sarcomas”- LPS and LMS

Trabectedin vs Dacarbazine for LPS and LMS, Phase 3

- HR for progression 0.55, P<.001
- Median PFS 4.2 mos vs 1.5 mos

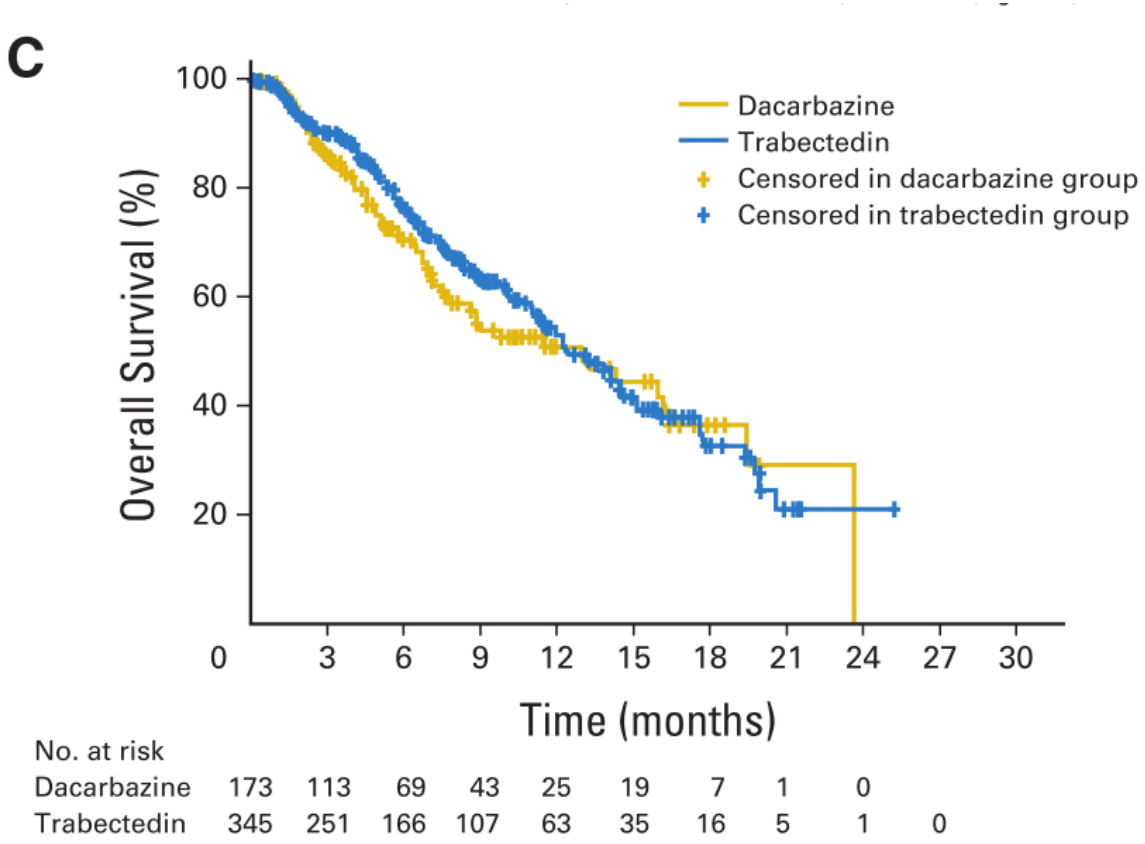


Demetri et al, JCO, 2015

Trabectedin vs Dacarbazine for LPS and LMS, Phase 3

- Did not meet OS endpoint
- Response Rate of 9.9% vs 6%
- Median OS 12.4 vs 12.9 months

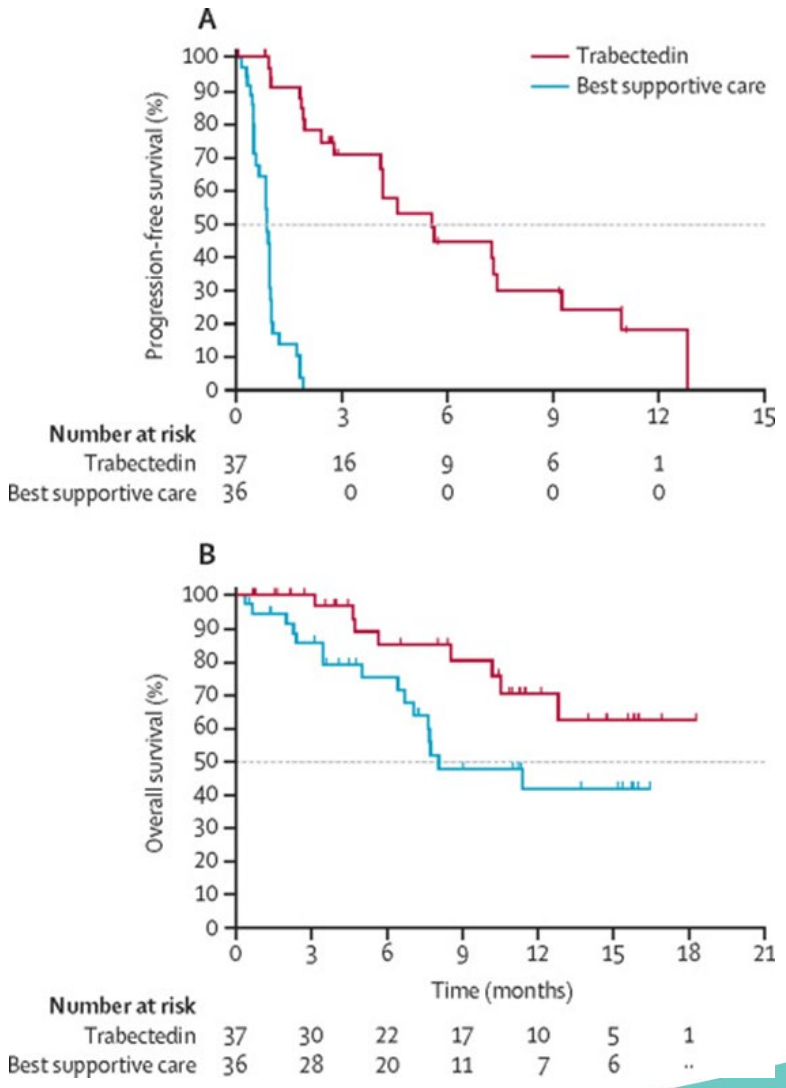
- Approved by FDA in November 2015 based on PFS benefit



Demetri et al, JCO, 2015

Trabectedin for translocation sarcoma, Phase 2 vs BSC

- Not an FDA approved indication, but will usually be able to get insurance coverage due to this study
- Ex/ synovial sarcoma, myxoid round cell liposarcoma
- FDA approved for leiomyosarcoma and liposarcoma



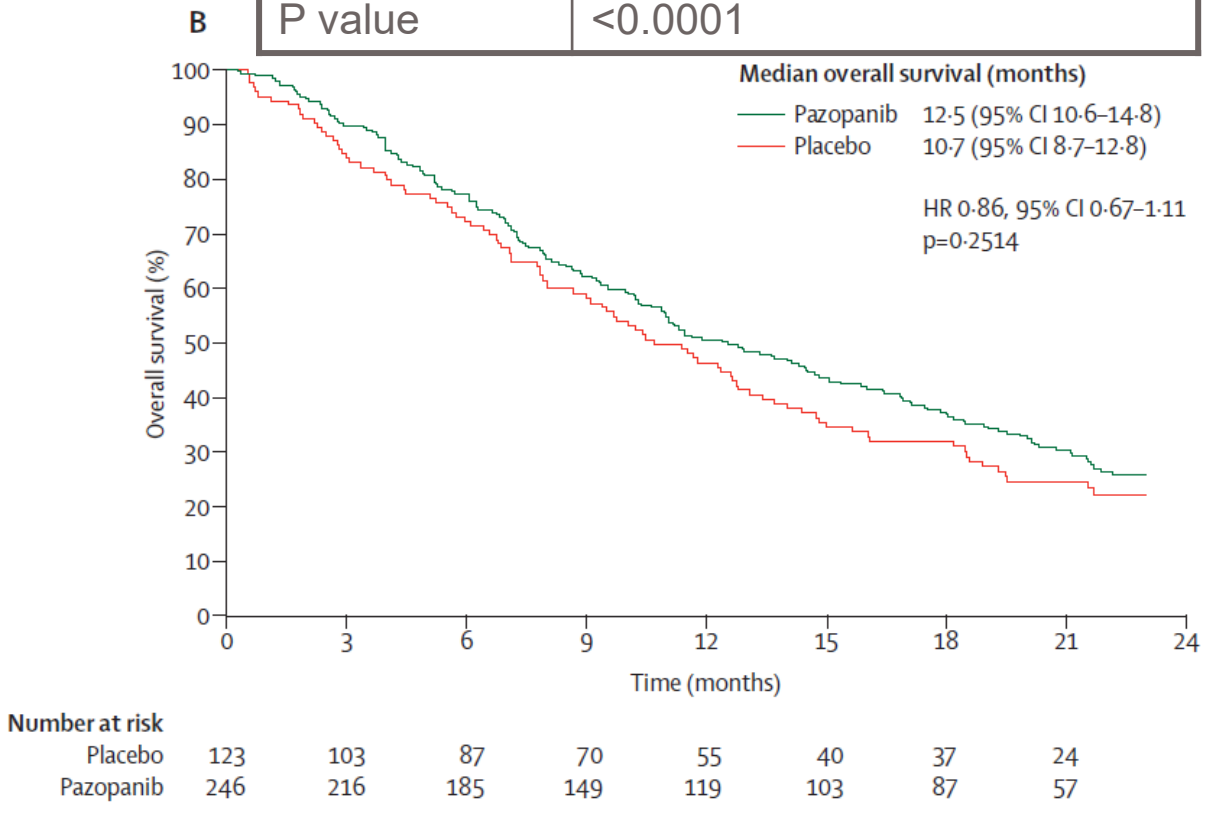
Kawai et al, Lancet Oncology, 2015

Pazopanib

- Multi-targeted TKI
- Trend towards improved OS
- ORR 6%,
- 67% with stable disease as best response

***not approved for liposarcoma**

	Placebo	Pazopanib
Median (months)	1.5	4.6
Hazard ratio (95%CI)	1	0.31 (0.24-0.4)
P value	<0.0001	



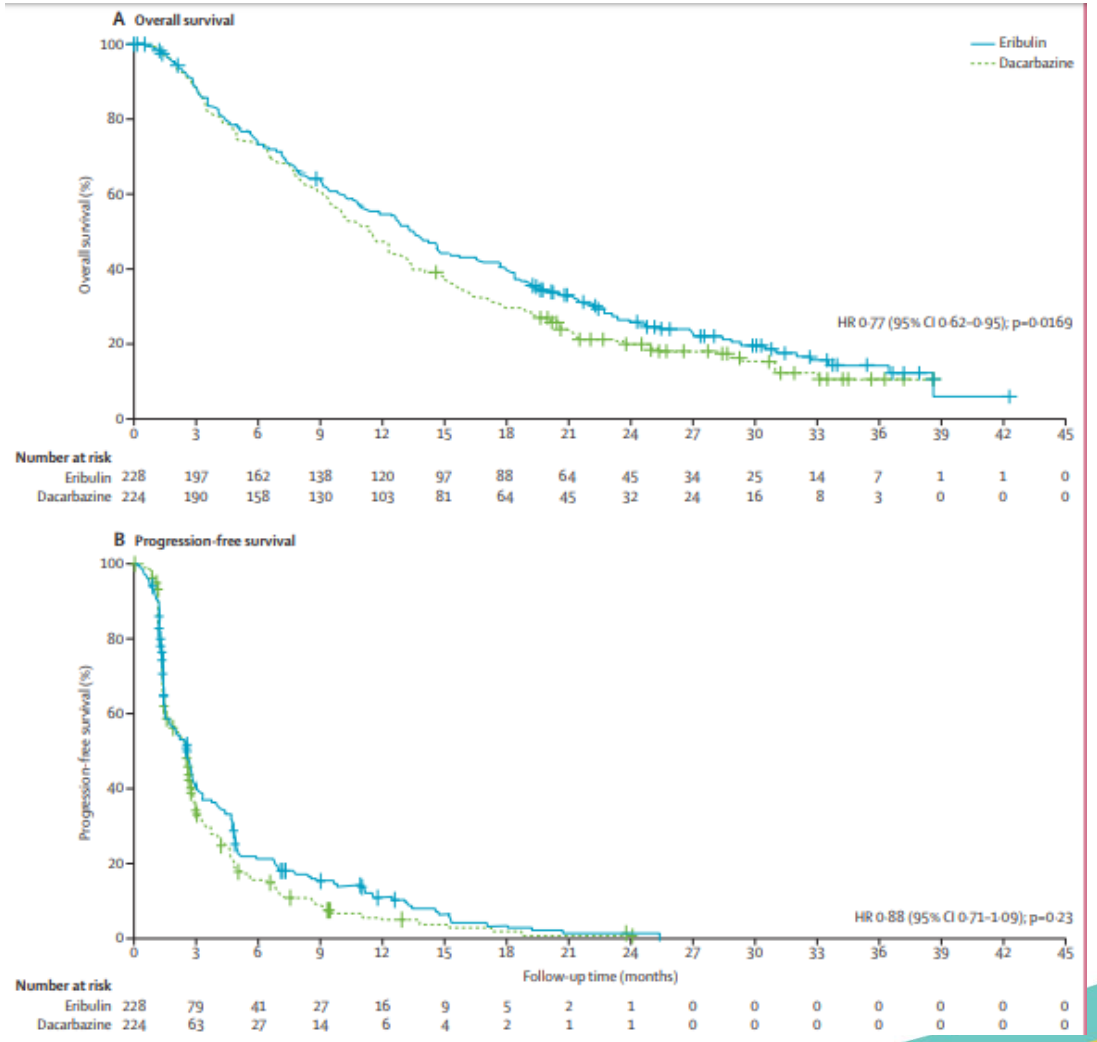
Van der Graaf, Lancet, 2012

Eribulin

- Phase II in sarcomas, prespecified endpoint of 12 mo PFS >30%

- Phase III
  - Included LPS and LMS only based on Phase II

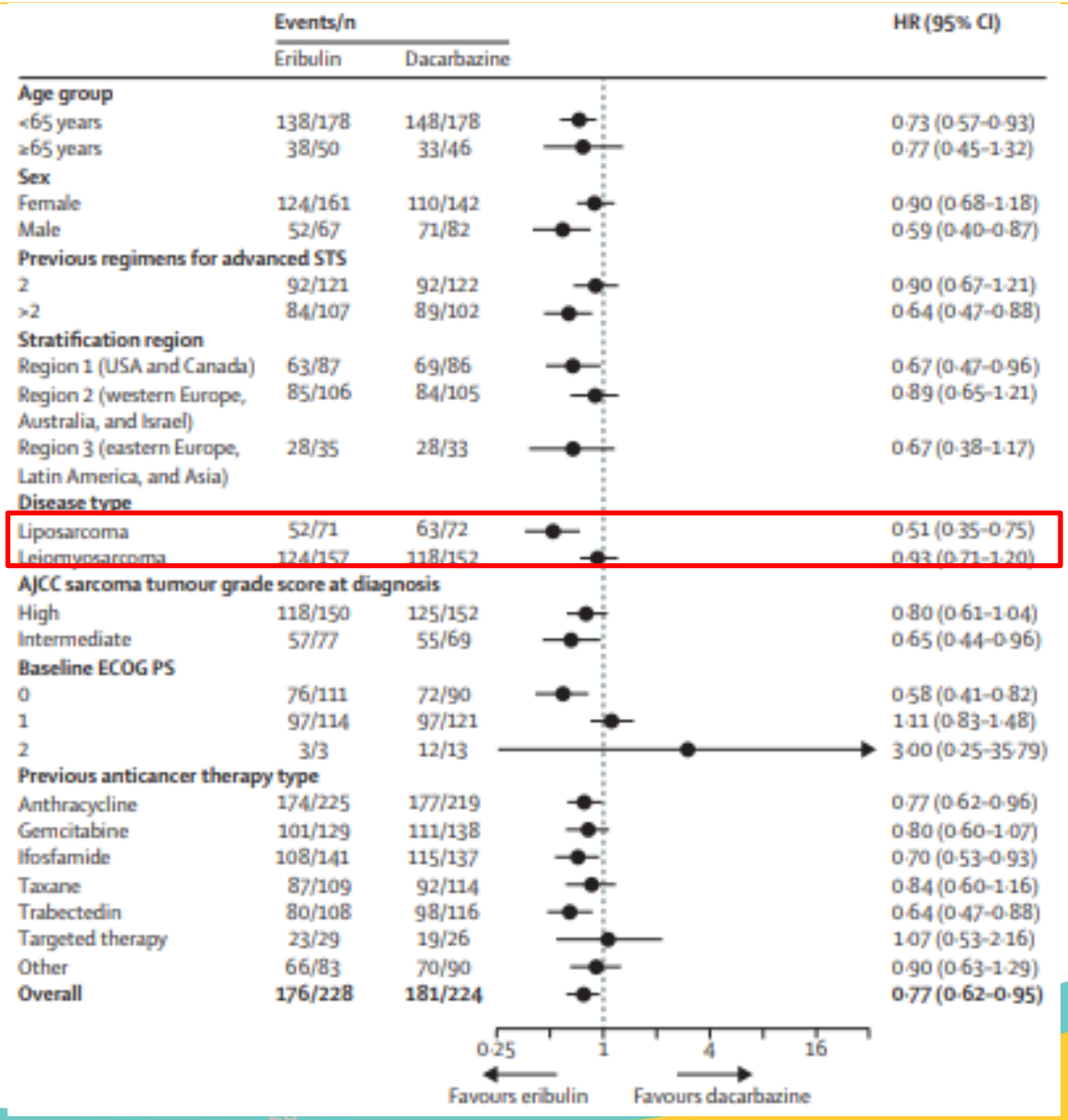
- OS benefit 13.5 mos vs 11.5 mos (p = 0.0169)
- No PFS benefit, 2.6 months in both groups, HR 0.88



Schöffski et al., Lancet 2016

Eribulin

- FDA approved for liposarcoma only after failure of 2 prior lines of therapy

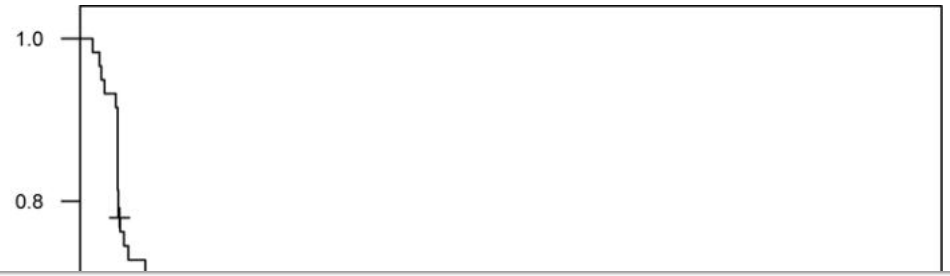


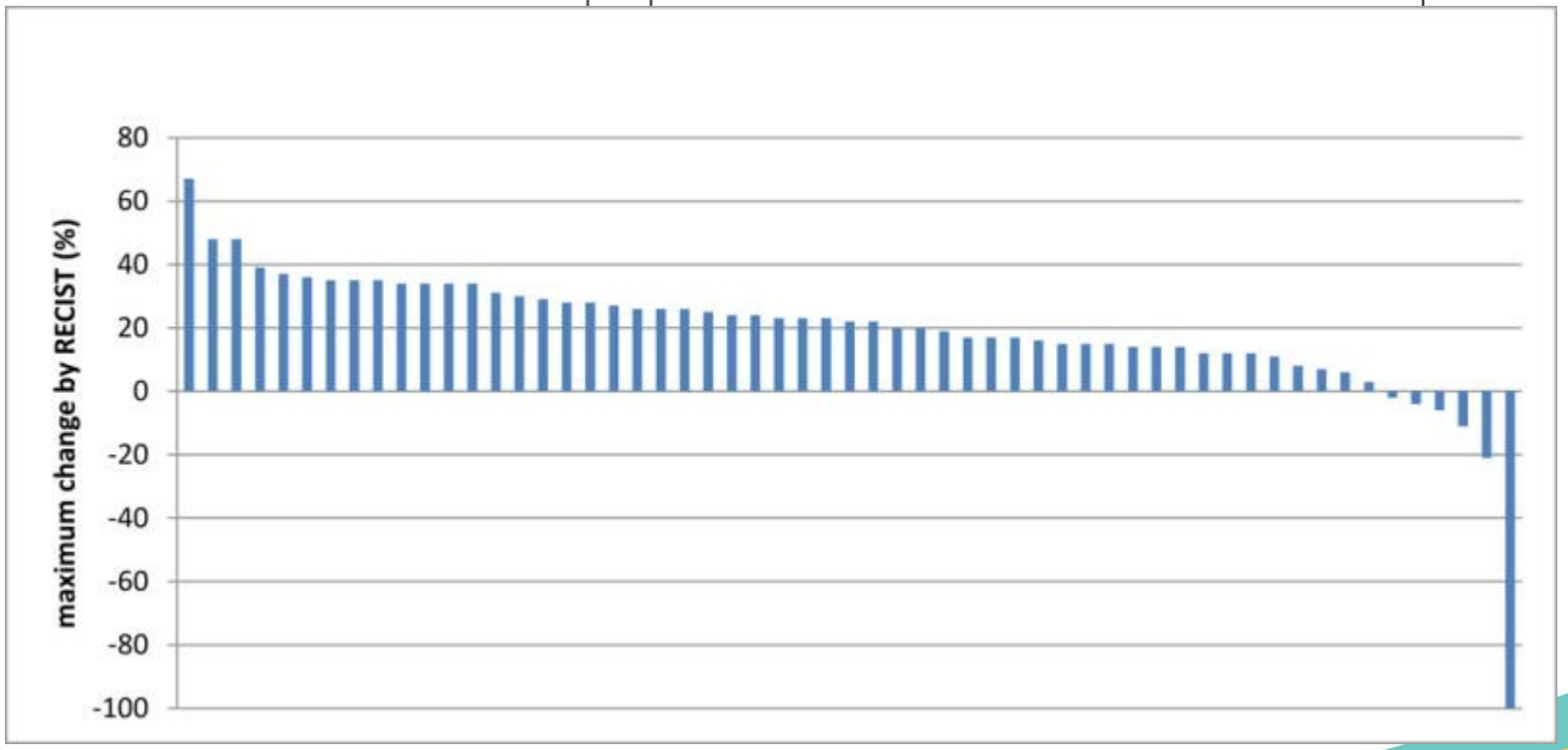
	Events/n		HR (95% CI)
	Eribulin	Dacarbazine	
Age group			
<65 years	138/178	148/178	0·73 (0·57–0·93)
≥65 years	38/50	33/46	0·77 (0·45–1·32)
Sex			
Female	124/161	110/142	0·90 (0·68–1·18)
Male	52/67	71/82	0·59 (0·40–0·87)
Previous regimens for advanced STS			
2	92/121	92/122	0·90 (0·67–1·21)
>2	84/107	89/102	0·64 (0·47–0·88)
Stratification region			
Region 1 (USA and Canada)	63/87	69/86	0·67 (0·47–0·96)
Region 2 (western Europe, Australia, and Israel)	85/106	84/105	0·89 (0·65–1·21)
Region 3 (eastern Europe, Latin America, and Asia)	28/35	28/33	0·67 (0·38–1·17)
Disease type			
Liposarcoma	52/71	63/72	0·51 (0·35–0·75)
Leiomyosarcoma	124/157	118/152	0·93 (0·71–1·20)
AJCC sarcoma tumour grade score at diagnosis			
High	118/150	125/152	0·80 (0·61–1·04)
Intermediate	57/77	55/69	0·65 (0·44–0·96)
Baseline ECOG PS			
0	76/111	72/90	0·58 (0·41–0·82)
1	97/114	97/121	1·11 (0·83–1·48)
2	3/3	12/13	3·00 (0·25–35·79)
Previous anticancer therapy type			
Anthracycline	174/225	177/219	0·77 (0·62–0·96)
Gemcitabine	101/129	111/138	0·80 (0·60–1·07)
Ifosfamide	108/141	115/137	0·70 (0·53–0·93)
Taxane	87/109	92/114	0·84 (0·60–1·16)
Trabectedin	80/108	98/116	0·64 (0·47–0·88)
Targeted therapy	23/29	19/26	1·07 (0·53–2·16)
Other	66/83	70/90	0·90 (0·63–1·29)
Overall	**176/228**	**181/224**	**0·77 (0·62–0·95)**

Schöffski et al., Lancet 2016

CD4/6 Inhibitors

- **Palbociclib 125 mg PO 21D/28D cycle**



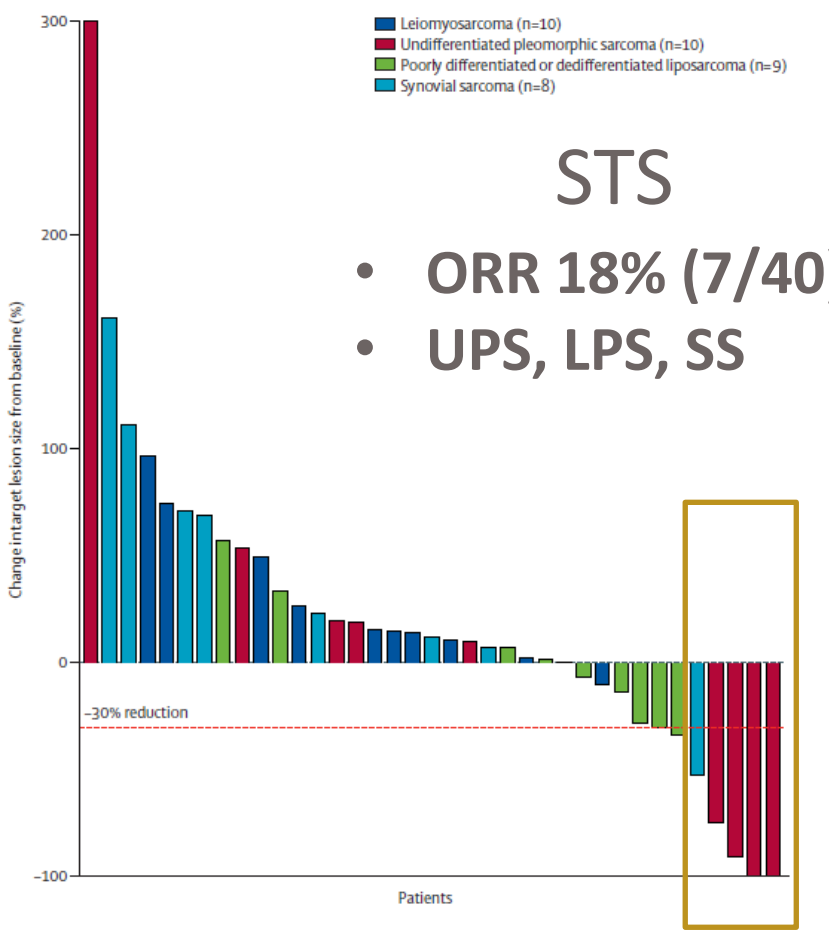


Dickson et al, JAMA Onc, 2016

What about immunotherapy?

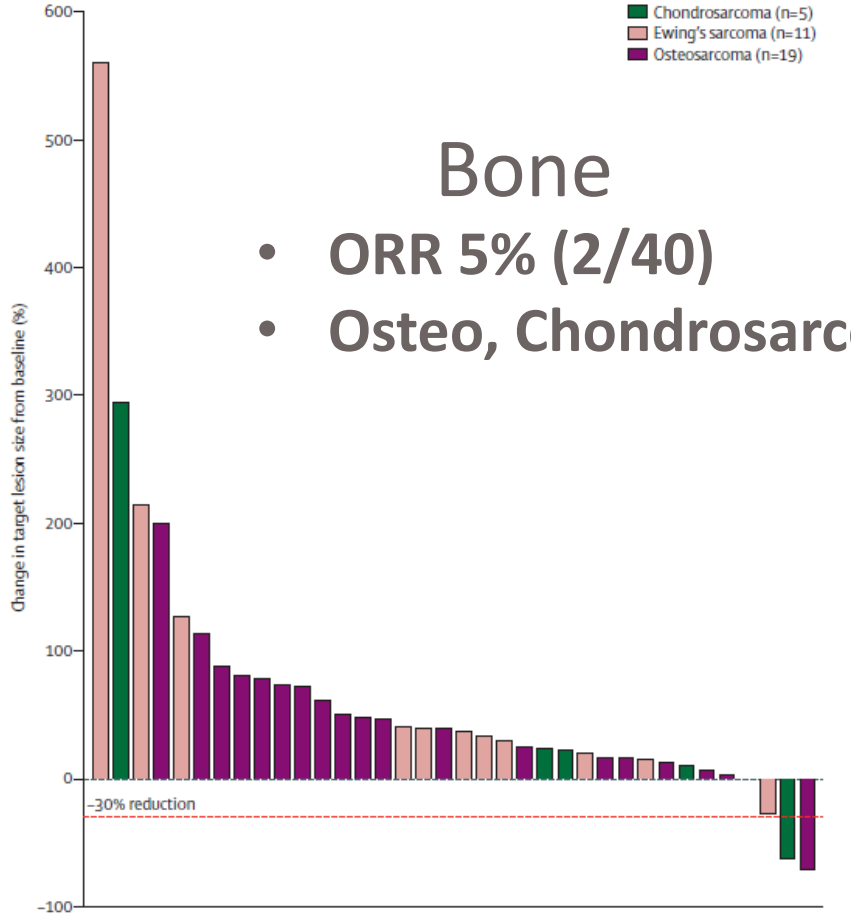
- Actively being studied
  - Pembrolizumab
  - Nivolumab +/- Ipilimumab
- Sarcoma is not an FDA approved indication for immunotherapy
- Many patients are interested in IO given the extensive media exposure

Responses with pembrolizumab



STS

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



Bone

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

- **Pembrolizumab on NCCN guidelines for UPS**

Tawbi et al, Lancet Oncology, 2017

Overview

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

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

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%)
    - **D842V**- avapritinib
  - "WT"- 85% of GISTs in children and 10% in adults
    - SDH
    - BRAF
    - NF1
    - NTRK fusion
    - Other…

GIST Treatment

- Surgery

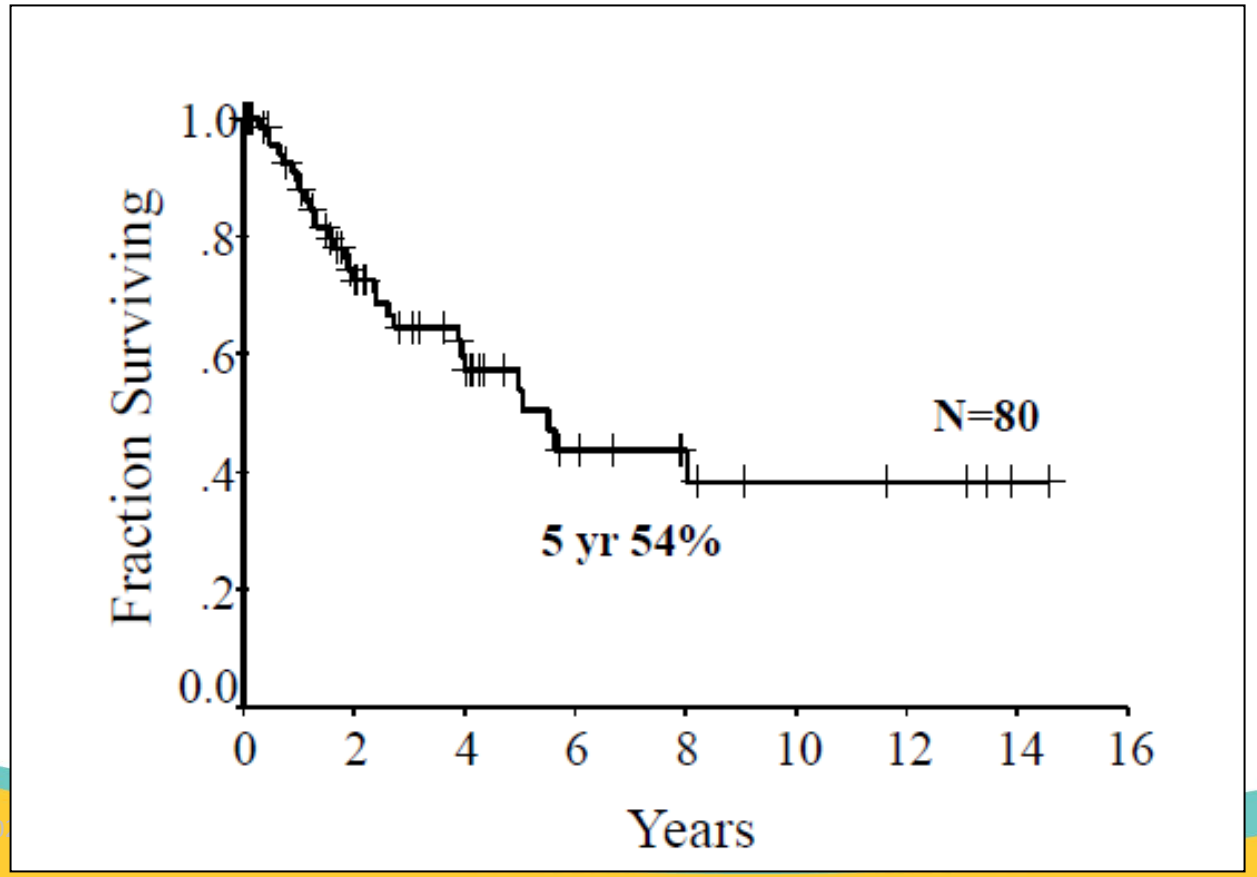
- Medicines
  - Tyrosine kinase inhibitors (TKIs)
  - Can be given before surgery if needed→ takes a long time (many months) before enough tumor shrinkage to get to surgery

- Rarely radiation

- Radiofrequency ablation (RFA), embolization, or chemoembolization

Historic Surgical Outcomes

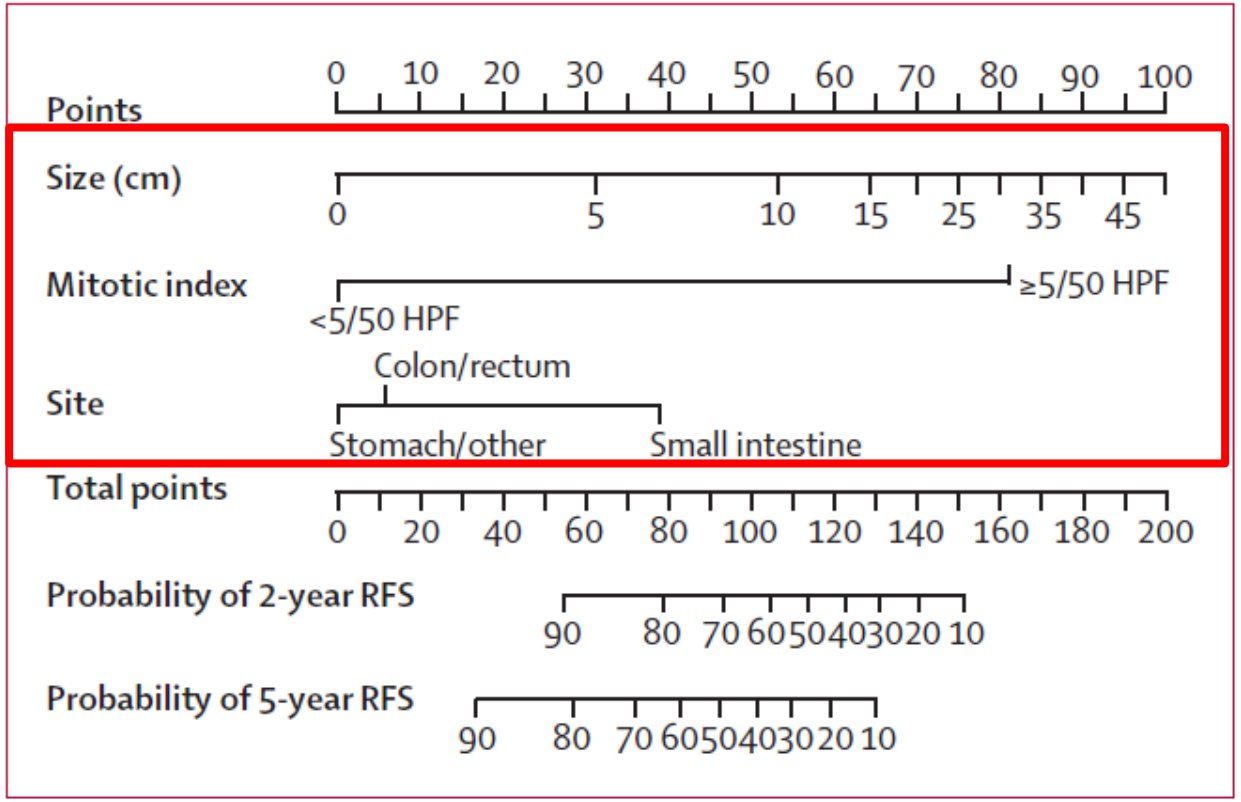
- 50% of patients can recur postoperatively, usually in the liver or peritoneum, and will die within 5 years **without additional treatment**



DeMatteo, *Ann Surg*, 2000.

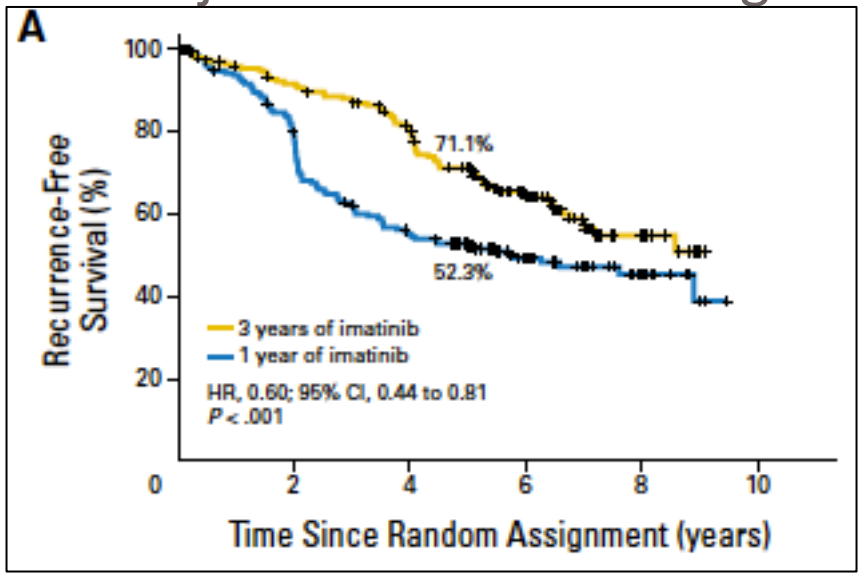
Predicting Postop Recurrence

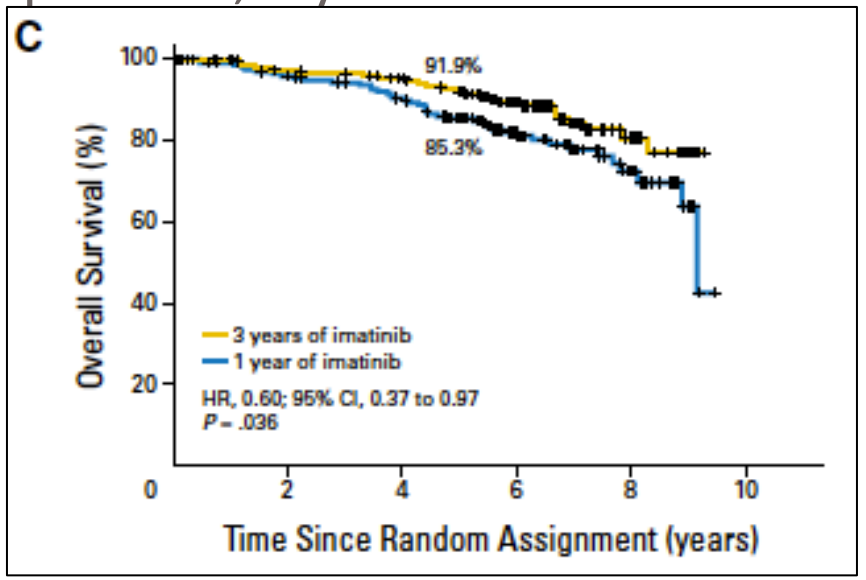
- **Who needs medicine after surgery?**



Medical Management: Adjuvant Therapy

- 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%

Joensuu, *J Clin Onc*, 2014.

Medical Management: Adjuvant Therapy

- At least 3 years of treatment after surgery for a high risk GIST is considered standard

- In the adjuvant setting the optimal treatment duration with imatinib is not known

- Although not formally studied in a published manuscript, many 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

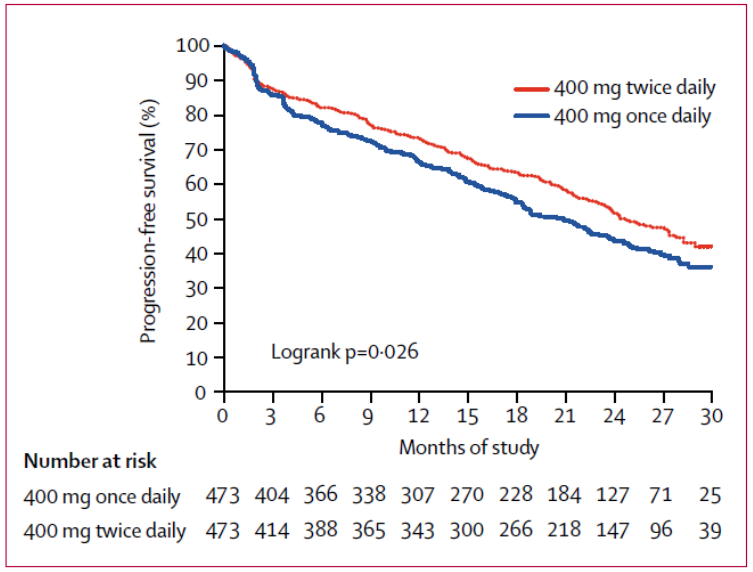
Medical Management: GIST Metastatic Disease

- Imatinib (or Avapritinib) → Sunitinib → Regorafenib → Ripretinib → Clinical Trial
- New ongoing studies may change this

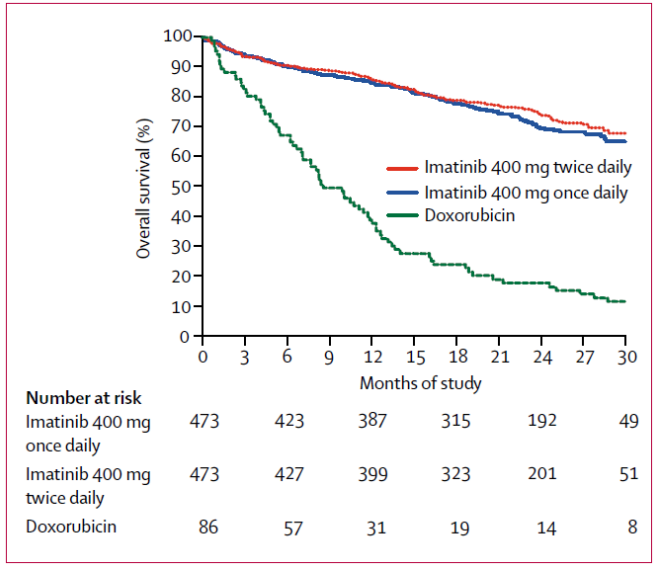
Medical Management: Metastatic Disease

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

1°: Progression-free Survival



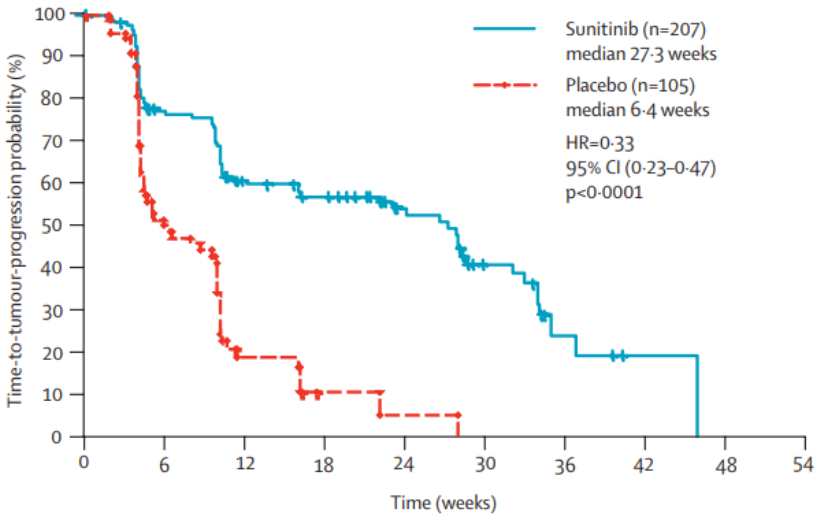
2°: Overall Survival



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

Medical Management: 2nd Line Metastatic Disease

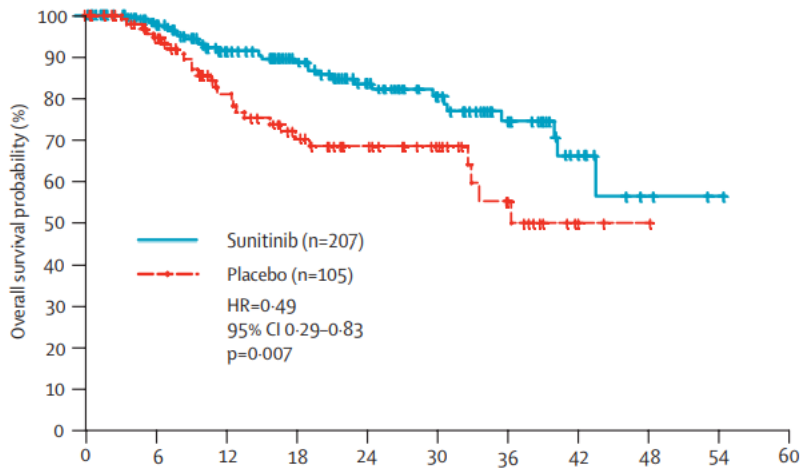
- 2nd line: sunitinib (Demetri 2006)



Number at risk

Sunitinib	207	106	67	53	34	18	5	1	0
Placebo	105	36	9	2	1	0	0	0	0

Improved Progression Free Survival



Number at risk

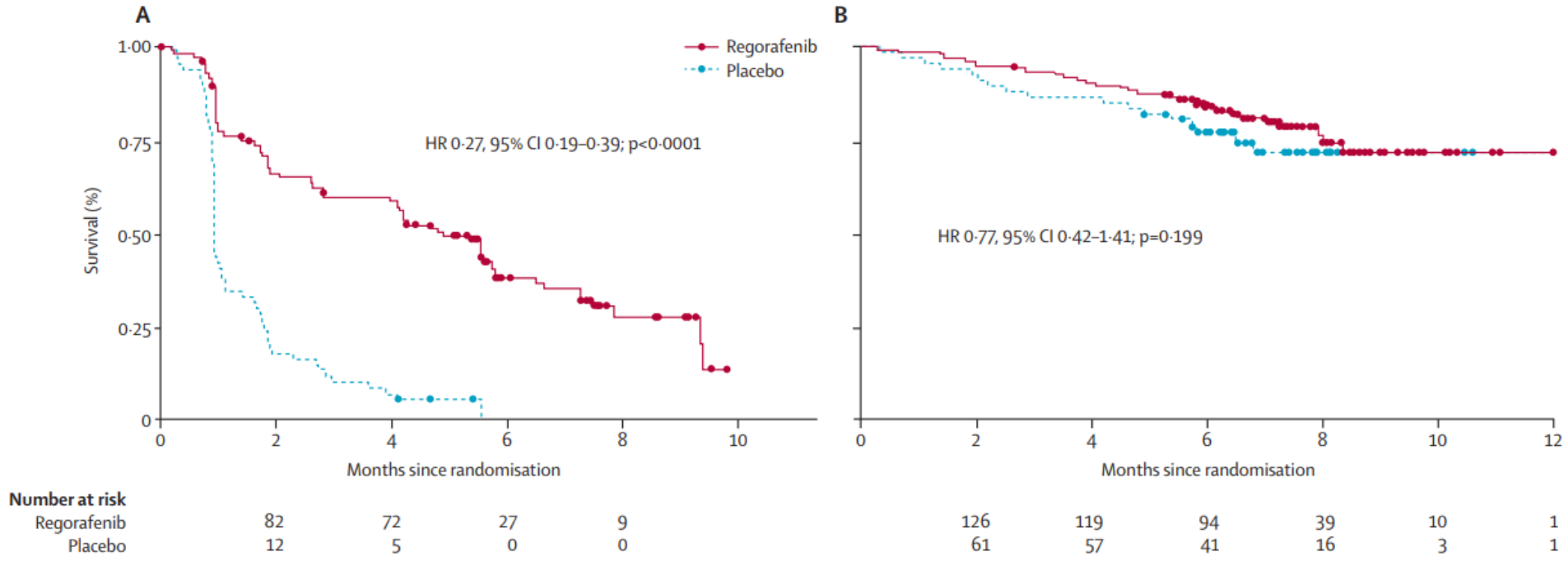
Sunitinib	207	167	117	97	71	50	31	11	3	1	0
Placebo	105	85	57	43	31	22	13	3	1	0	0

Improved Overall Survival

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

Medical Management: 3rd Line Metastatic Disease

- 3rd line: Regorafenib (Demetri 2013)



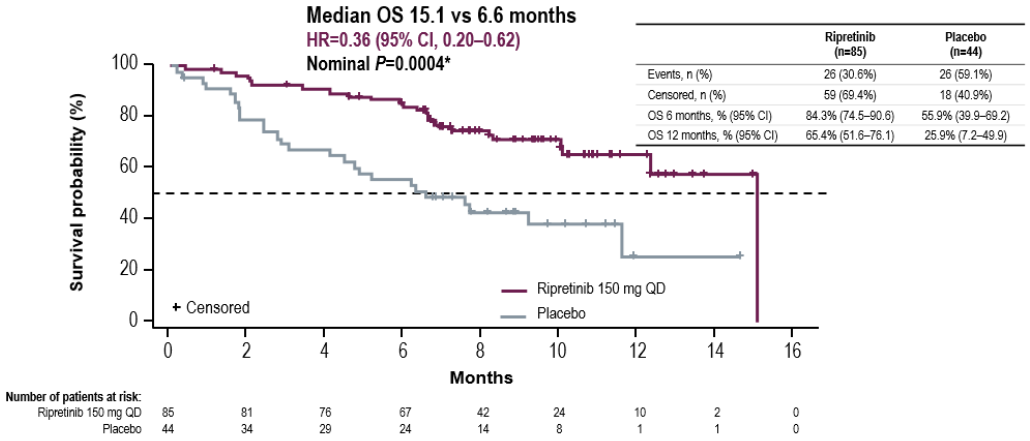
Improved Progression Free Survival

Improved Overall Survival

Medical Management: GIST Metastatic Disease

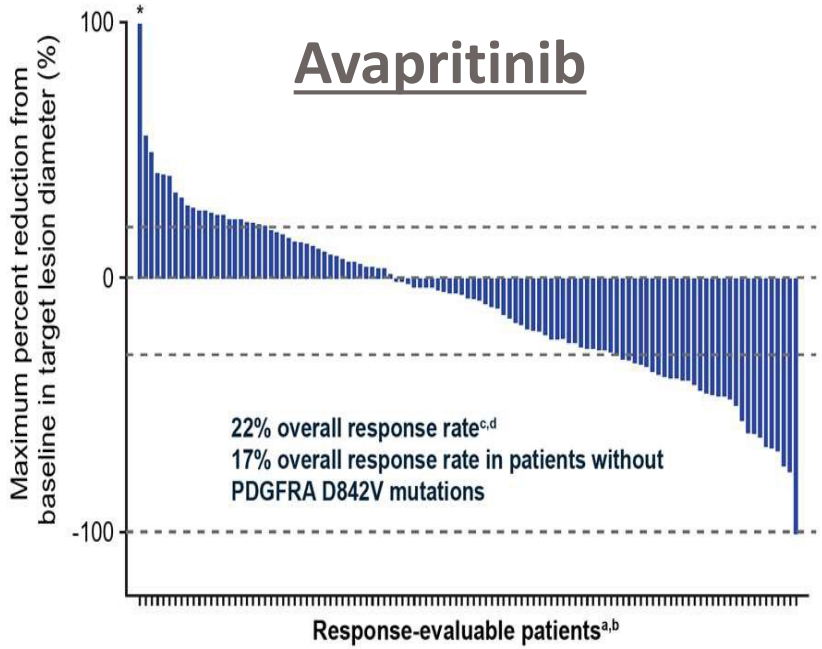
- 4th Line and beyond (Ripretinib recently approved)

Ripretinib



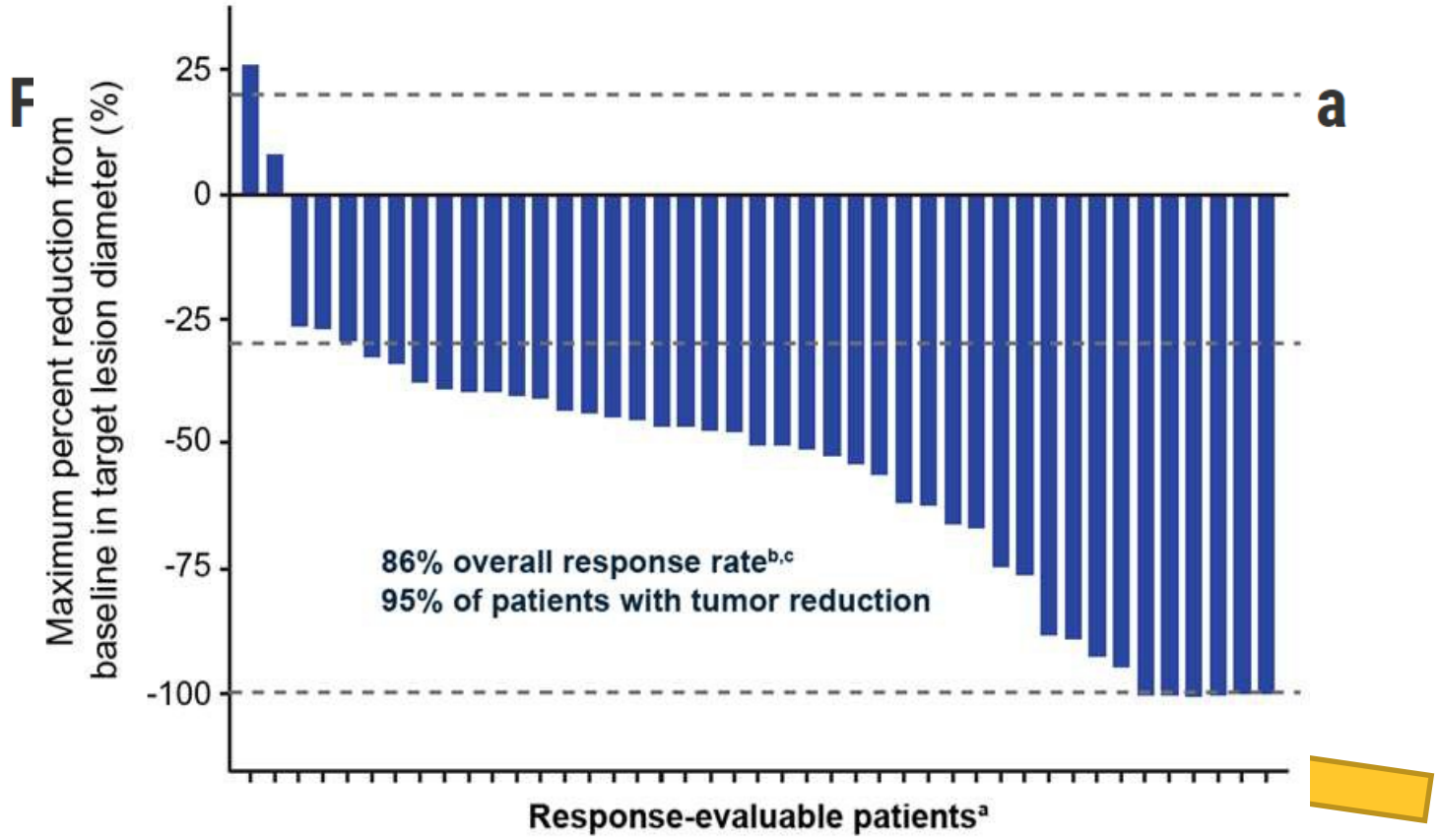
	Ripretinib (n=85)	Placebo (n=44)
Events, n (%)	26 (30.6%)	26 (59.1%)
Censored, n (%)	59 (69.4%)	18 (40.9%)
OS 6 months, % (95% CI)	84.3% (74.5–90.6)	55.9% (39.9–69.2)
OS 12 months, % (95% CI)	65.4% (51.6–76.1)	25.9% (7.2–49.9)

Avapritinib



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

Medical Management: GIST Metastatic Disease



growing.

- **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
  - 1st choice usually Imatinib 400 mg daily
  - Sunitinib, Regorafenib, Ripretinib
  - Avapritinib for PDGFRa D842V mutation
  - No role for standard chemotherapy

Medical Management: Bone/Pediatric Sarcomas

- Osteosarcoma
  - MAP-surgery-MAP
- Ewing sarcoma
  - ddVDC/IE – XRT/surgery – ddVDC/IE
- Rhabdomyosarcoma
  - Alveolar/Embryonal/spindle cell/sclerosing subtypes
  - Risk stratification, ALL REQUIRE MULTI-AGENT CHEMOTHERAPY
- Chondrosarcoma- Surgery if possible, not very responsive to chemo

Overview

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

Medical Management: Bone/Pediatric Sarcomas

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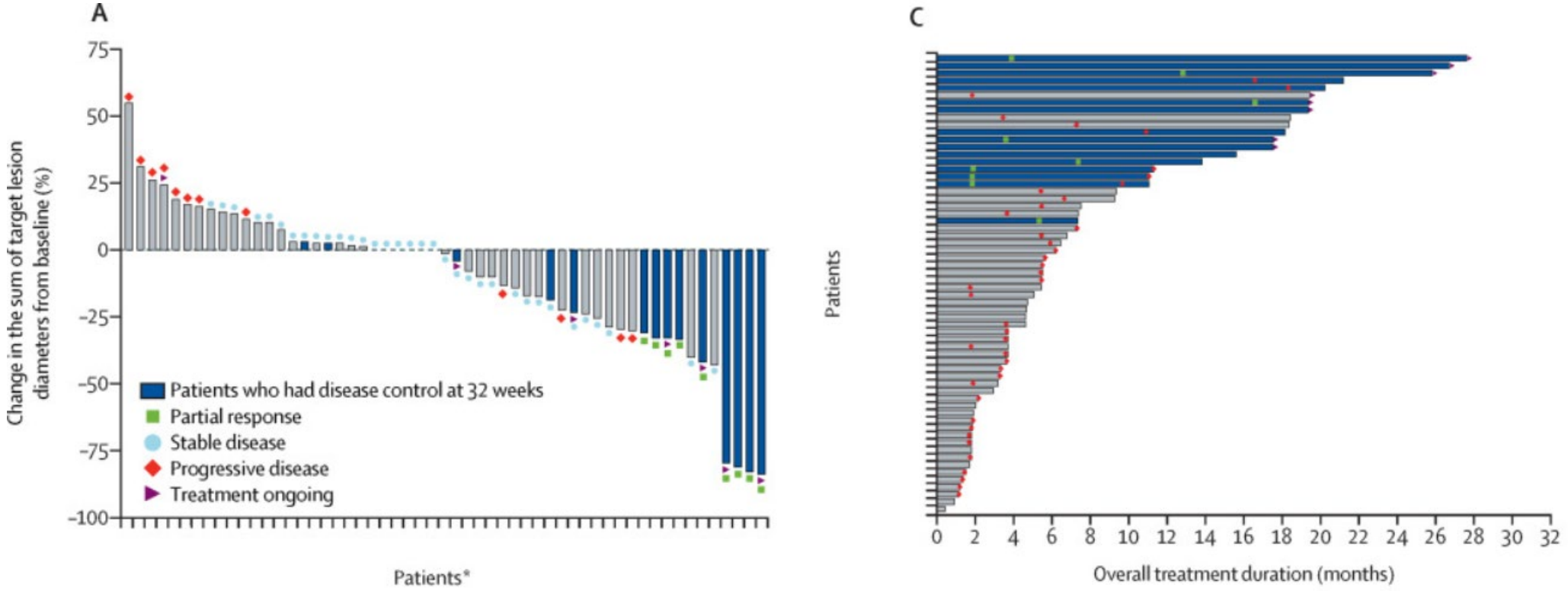
Special Other Histologies (simply recognizing the disease entity is a possible boards question)

- **Angiosarcoma- highly responsive to taxanes
- Dermatofibrosarcoma Protuberans (DFSP)- imatinib
- PVNS- Pexidartinib (CSF1R inhibition)
- **Desmoid- sorafenib, imatinib (assoc with FAP)
- Giant Cell Tumor of Bone- denosumab
- Inflammatory myofibroblastic tumor (IMT)- if ALK positive, can respond to crizotinib
- PEComa- mTOR inhibitors
- **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 approved for epithelioid sarcoma**

Gounder et al, Lancet Onc 2020

Summary

- STS Neoadjuvant/adjuvant therapy
  - Surgery and radiation for most STS of extremity, surgery alone for STS of abdomen/RP
- STS Metastatic disease
  - Doxorubicin, increasingly histiotype tailored systemic tx
- GIST
  - Risk stratification after surgery, 3 yrs adjuvant imatinib
  - Imatinib->sunitinib-> Regorafenib-> Ripretinib
- Bone/other
  - Multiagent chemotherapy for Ewing/Osteosarcoma

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

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