Sarcomas:
An Overview

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Disclosures

Research Funding to Institution

- Tracon
- AADi
- Eli Lilly
- Advenchen
- Iterion
- Blueprint
- Exelixis
- CBA Research
- Philogen
- Gradalis
- Monopar
- Avacta

Advisory Board Participation

- AADi
- Avacta

Outline

- General Sarcoma Background
- Doxorubicin
- Other Systemic Therapy Agents
- Targeted Therapies
- ImmunoTherapeutics
- Gastrointestinal Stromal Tumors

Sarcoma

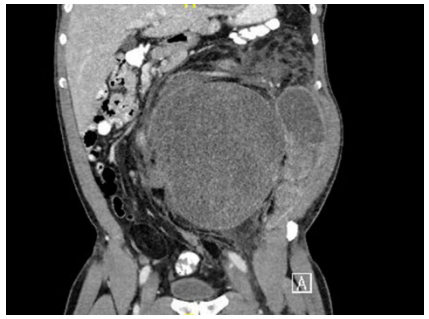
- Plural: *sarcomas* or *sarcomata*
- 1650s, "fleshy excrescence," from Greek *sarkoma* "fleshy substance"
- A "harmful tumor of the connective tissue," more or less malignant (Abernethy, 1804).
- Same root as *sarcasm*, "a biting taunt or gibe, a satirical remark or expression.”

Sarcoma Background

- **By The Numbers…**
  - 1% of solid tumors
  - Young population->Increased impact!
  - Long recognized as an area of unmet need.

Site	New Cases	Deaths
Soft Tissue	13,590	5,200
Bone	3,970	2,050
Total US 2024	17,560	7,250
GIST	4-6K	

- **Great Heterogeneity**
  - At least 173 different types.
    - "Sarcoma" is to mesenchymal tumors as "Carcinoma" is to epithelioid tumors.
  - Bone versus Soft Tissue.
  - Fusion protein: Yes (30%) vs. No (70%)
  - Anatomic: Trunk/extremities vs. Retroperitoneal



- **Risk Factors**
  - Genetics (Li-Fraumeni Syndrome)
  - Environmental Factors (Herbicides, prior radiation)
  - Unknown in most cases

Siegal 2024. CA: Cancer J Clin 74: 12-49
https://www.cancer.org/cancer/types/gastrointestinal-stromal-tumor/about/key-statistics.html
Sarcoma Progress Review Group. A Roadmap for Sarcoma Research. *Sarcoma Progress Review Group Roundtable Meeting*: National Cancer Institute, U.S. Department of Health and Human Services, 2004. Avhttps://sarcomahelp.org/assets/2004roadmap.pdf.

Staging

- **“Stage” = “Stage at initial diagnosis”**
- **GRADE**/Primary Tumor/Node (uncommon)/Metastasis
- **American Joint Commission on Cancer 8th ed. (2017)**
  - Soft Tissue Sarcoma Sub-Staging Systems
    - Head/Neck (No I-IV)
    - Extremities/Trunk
    - Thoracic/Abdominal Viscera (No I-IV)
    - Retroperitoneal
    - Gastrointestinal Stromal Tumors (GIST)
  - Bone
- 5-Year Survival
  - I 80-100% (Typically low-grade)
  - II 60-80% (Not low-grade)
  - III 30-50% (Not low-grade)
  - IV <20% (anatomic definition)

Sarcoma Drug	Year of FDA Approval
Doxorubicin*	1974
Dacarbazine	1975
Ifosfamide	1988
Liposomal Doxorubicin* (Kaposi's)	1995
Gemcitabine	1996
Pazopanib*	2009
Eribulin* (Liposarcomas)	2010
Trabectedin* (L-sarcomas)	2015
Denosumab* (Giant Cell Tumor of Bone)	2018
Pexidartinib* (Tenosynovial Giant Cell Tumor)	2019
Tazemetostat* (Epithelioid sarcoma)	2020
Nab-sirolimus* (PEComa)	2022
Nirogacestat* (Desmoid Tumors)	2023
Afamitresgene autoleucel* (Synovial)	2024

Other Agents In Use

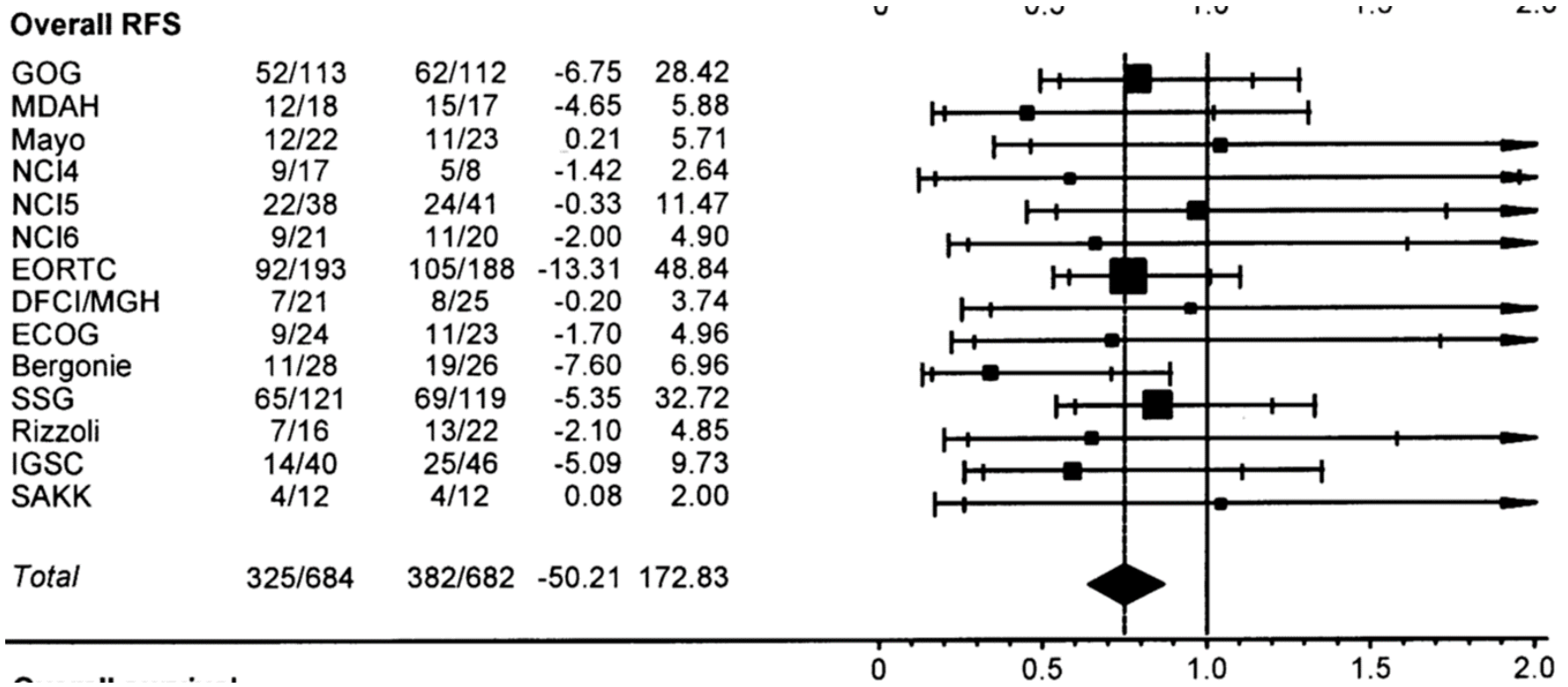
Temozolomide (Leiomyosarcoma)
Etoposide
Taxanes (Angiosarcoma)
Cisplatin/Methotrexate (Osteosarcoma)
Actinomycin-D/Vincristine (Ewing's, Rhabdo)
Sorafenib/Pazopanib (Desmoid tumors)

* Sarcoma as FDA-labeled indication.

Primary Treatment

- Surgery + Neoadjuvant/Adjuvant Radiotherapy
  - About 90% effective in achieving local cure.
  - Only about 50% effective overall
- Systemic Therapy
  - **Essential-Sarcomas of Childhood-Major Contribution to Curability!!!**
    - **Osteosarcoma**
    - **Ewing's sarcoma**
    - **Alveolar/Embryonal Rhabdomyosarcoma**
  - Other Soft Tissue Sarcoma-Controversial
    - Probably some modest benefit (<10%?) in treating micrometastatic disease
    - Utility in improving resectability in difficult cases

Adjuvant Chemotherapy

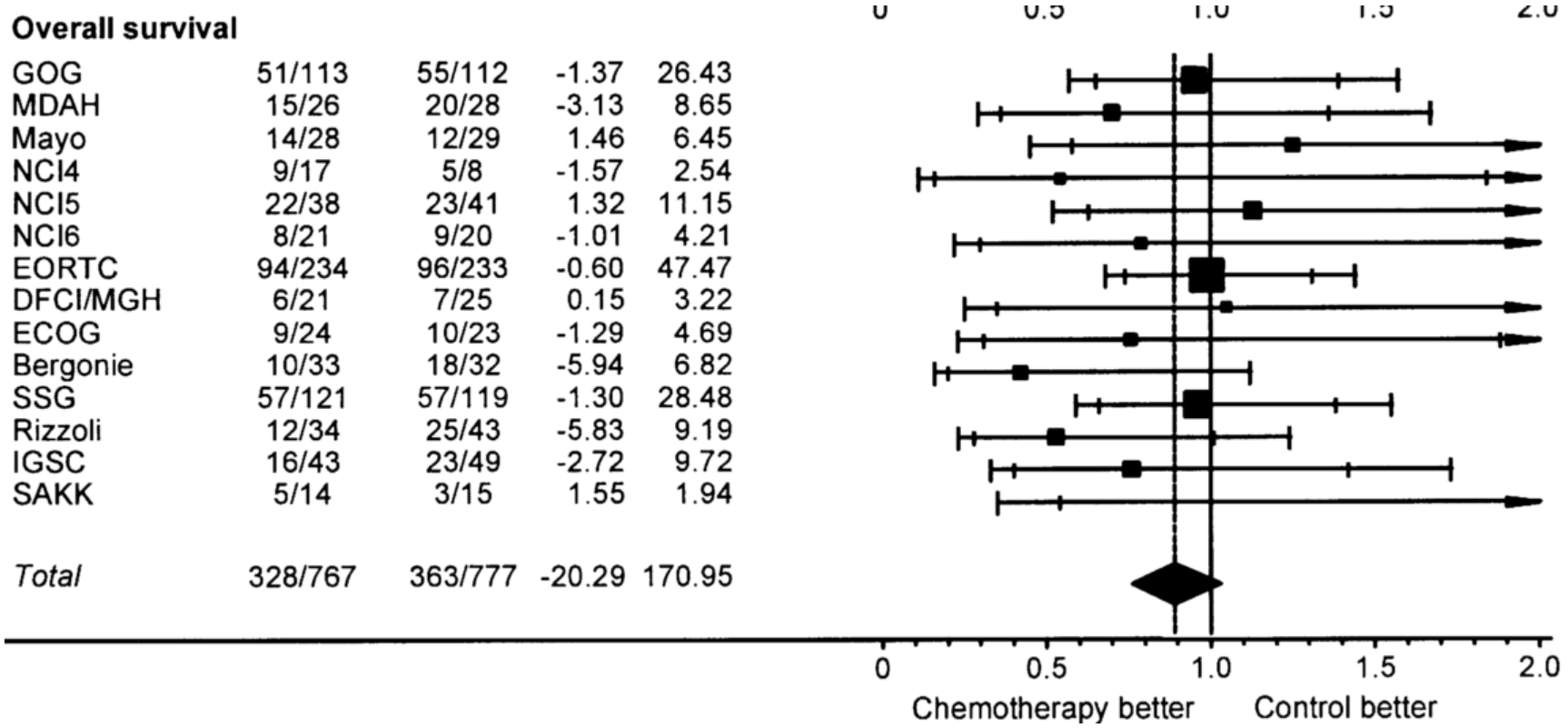


Overall RFS				
GOG	52/113	62/112	-6.75	28.42
MDAH	12/18	15/17	-4.65	5.88
Mayo	12/22	11/23	0.21	5.71
NCI4	9/17	5/8	-1.42	2.64
NCI5	22/38	24/41	-0.33	11.47
NCI6	9/21	11/20	-2.00	4.90
EORTC	92/193	105/188	-13.31	48.84
DFCI/MGH	7/21	8/25	-0.20	3.74
ECOG	9/24	11/23	-1.70	4.96
Bergonie	11/28	19/26	-7.60	6.96
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

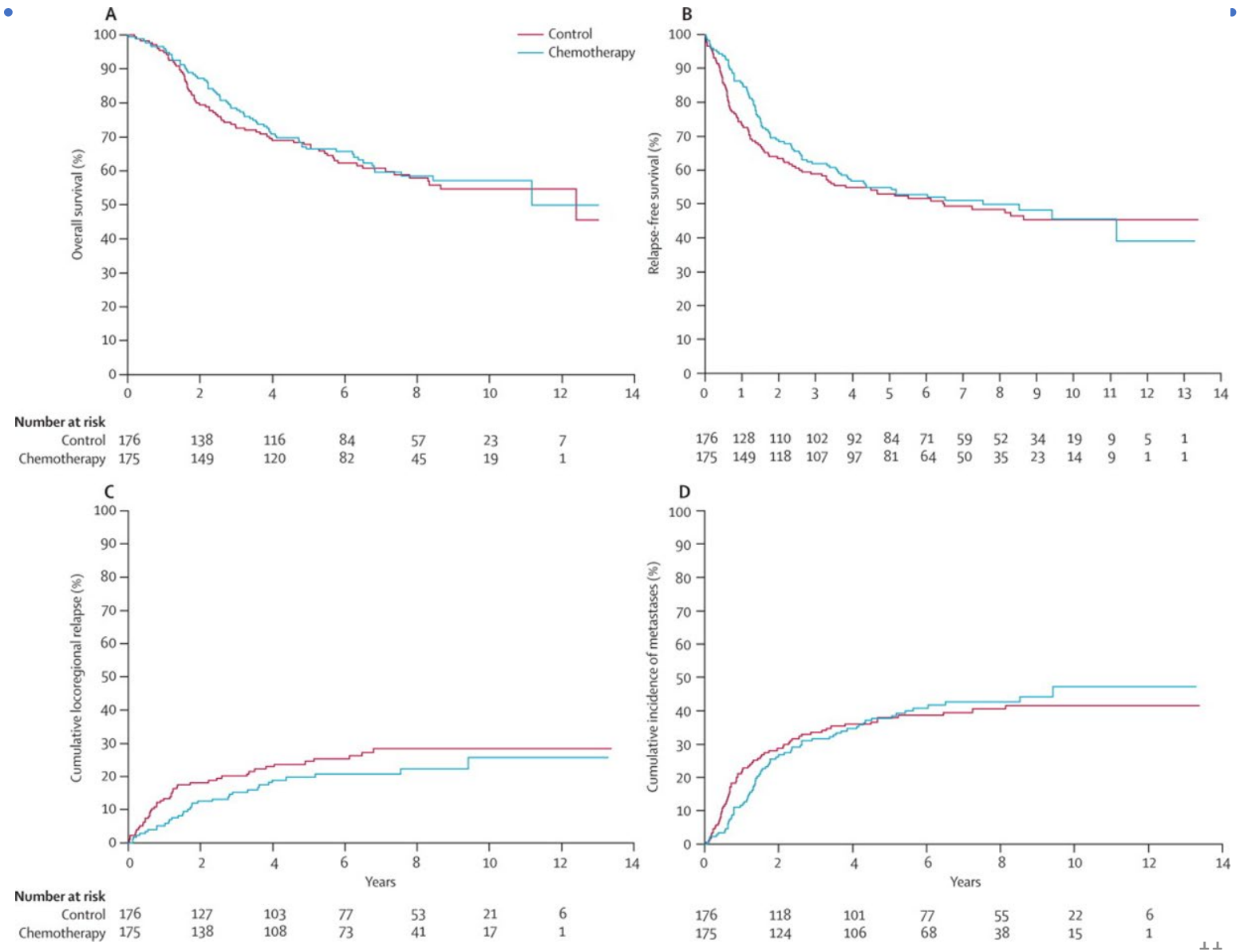


- **"Trend" but not significant improvement in OS**

SMAC, Lancet 1997

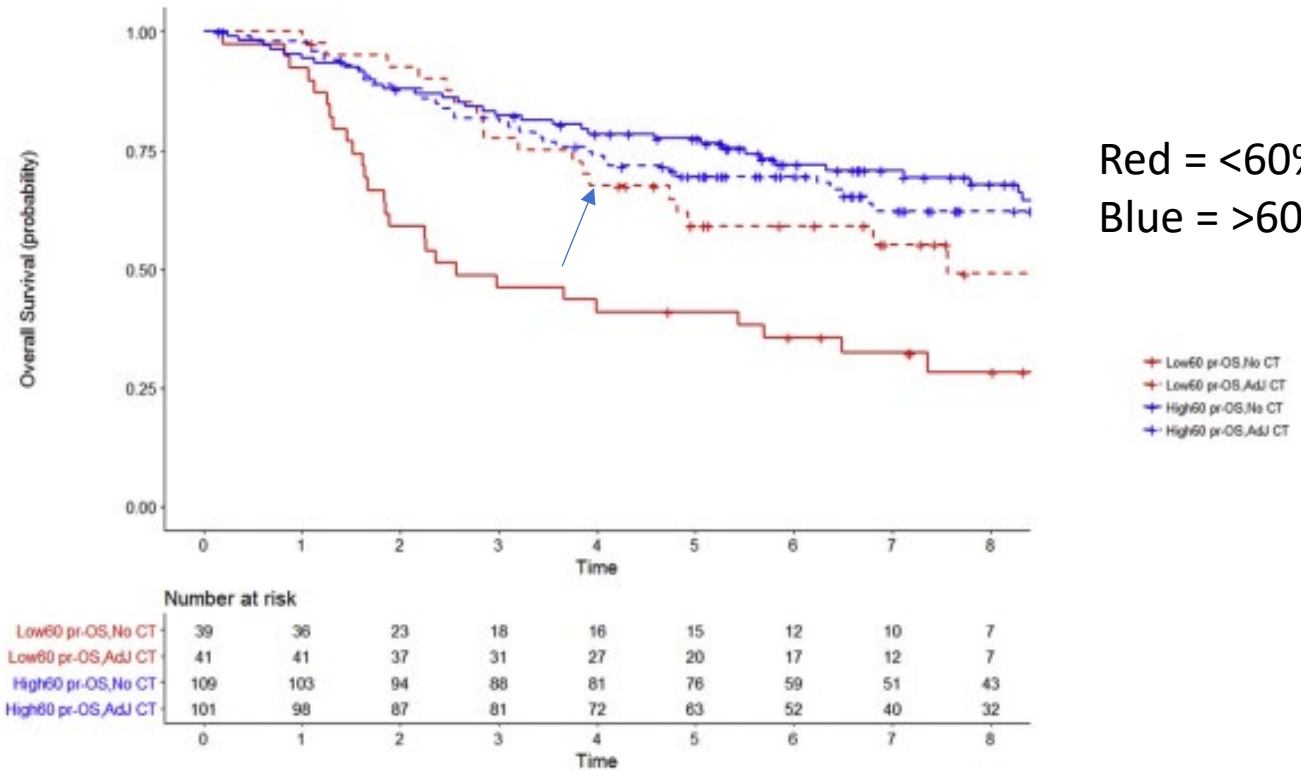
Adjuvant Chemotherapy: EORTC study

- **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

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



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

- Chemotherapy improves OS of highest risk patients
  - (but post hoc analysis….)

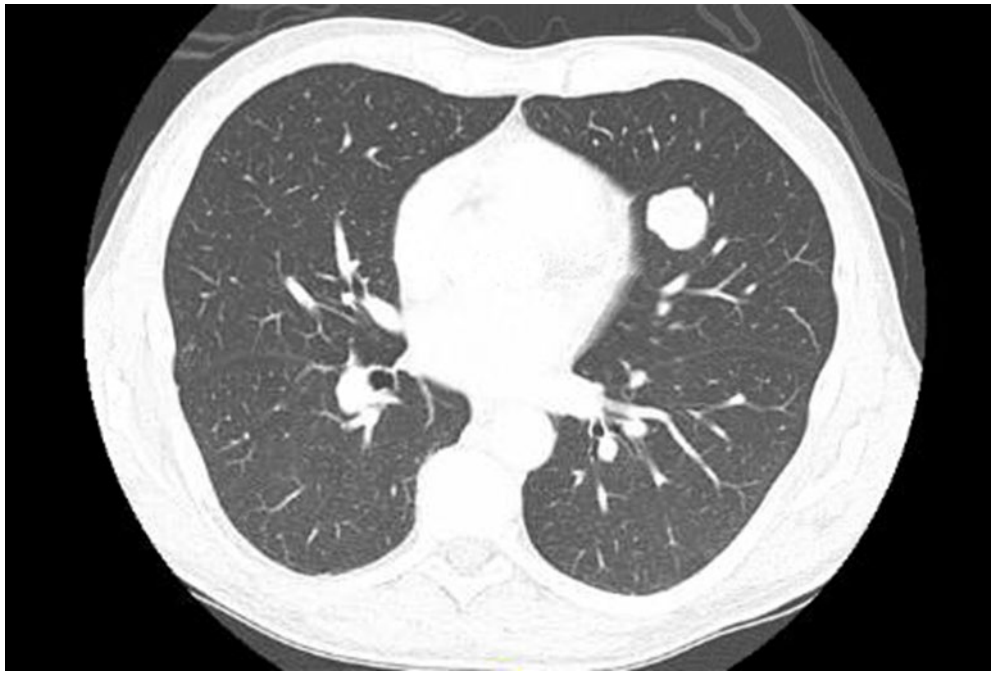
Pasquali et al, EJC, 2019
www.sarculator.com

Adjuvant Chemotherapy Summary

- Adjuvant chemo improved relapse free survival
- No significant benefit in OS
  - Histotype-Tailored?
- Controversial because many argue sub-par chemotherapy dosing and patient selection
- *Board answer: No adjuvant chemotherapy

SMAC, Lancet 1997
Gronchi et al., 2017. Lancet Oncol 18:812-822.
Slide adapted from R. Ratan

Advanced Disease

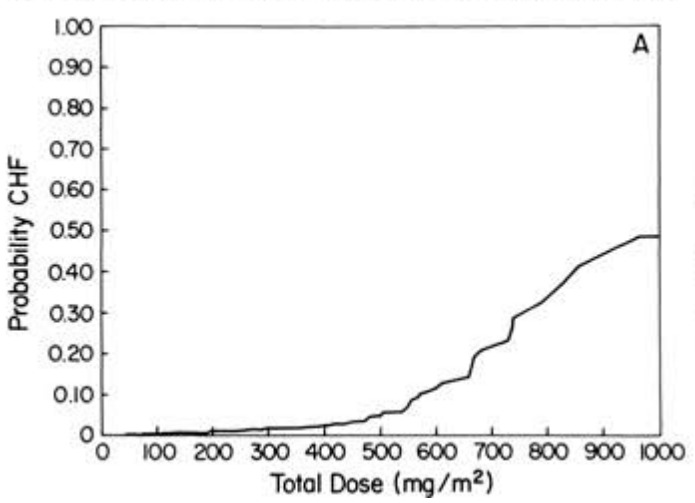


- Systematic Review 2021
- 1044 patients from 8 retrospective studies
- 5-yr OS 20-58%
- Factors associated with better OS
  - R0 resection
  - Smaller and lesser number of mets
  - Longer (>12m) disease-free interval

J Thorac Dis 2021;13(4):2649-2660 | http://dx.doi.org/10.21037/jtd-2019-pm-13

Doxorubicin/Adriamycin

- Approved in 1974
- Biosynthetic derivative of daunorubicin
- Triumph of search for anti-neoplastic natural products
  - *Streptomyces* derivative
  - Active at nM concentrations
- Broad anti-neoplastic spectrum
  - Activity not well defined prior to approval
- Dose-dependent cardiomyopathy
  - Limits total lifetime dosing
  - Dexrazoxane from C1 proposed to mitigate?[1]



Von Hoff 1979 Ann Intern Med 91:710

1) Van Tine et al., 2021. Clin Cancer Res 2021;27:3854–60.

Doxorubicin in Soft Tissue Sarcoma

- Meta-analysis[1]
  - 7 EORTC studies
  - Anthracycline regimens
  - 2233 patients
  - Median OS=51 wk
  - ORR=26%
- Control arm randomized trial[2]
  - Median OS=12.8m/51 wk
  - ORR=14%

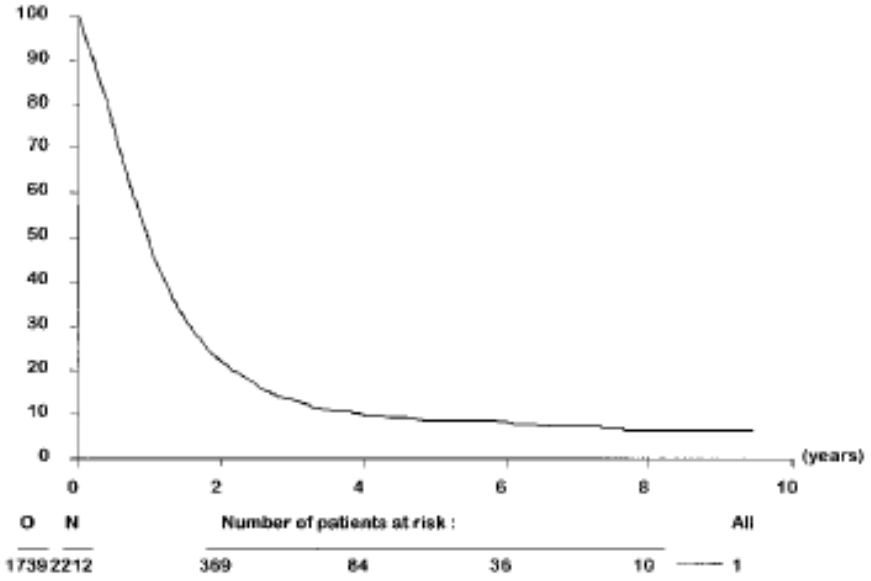


Fig 1. Overall survival. O, observed failures; N, total number of cases.

1) Van Glabbeke, 1999. JCO 17:150
2) Judson 2014. Lancet 15:415

Combination Therapy: Doxorubicin + Ifosfamide*

1995[1]

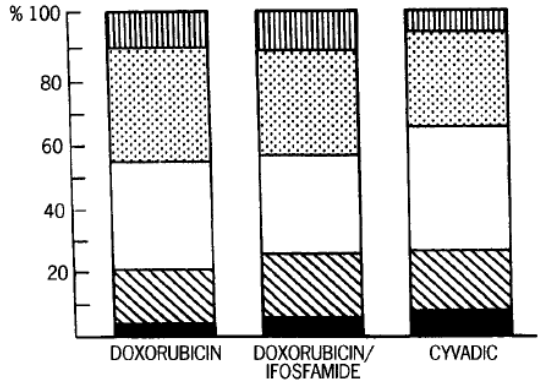


Fig 1. Response rate related to treatment. (■) Not assessable, including early death due to toxicity or other causes; (▨) progressive disease, including early death due to malignant disease; (□) no change; (▩) partial response; (■) complete response.

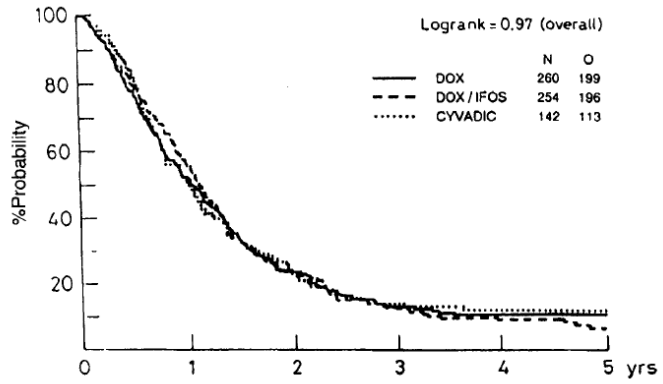
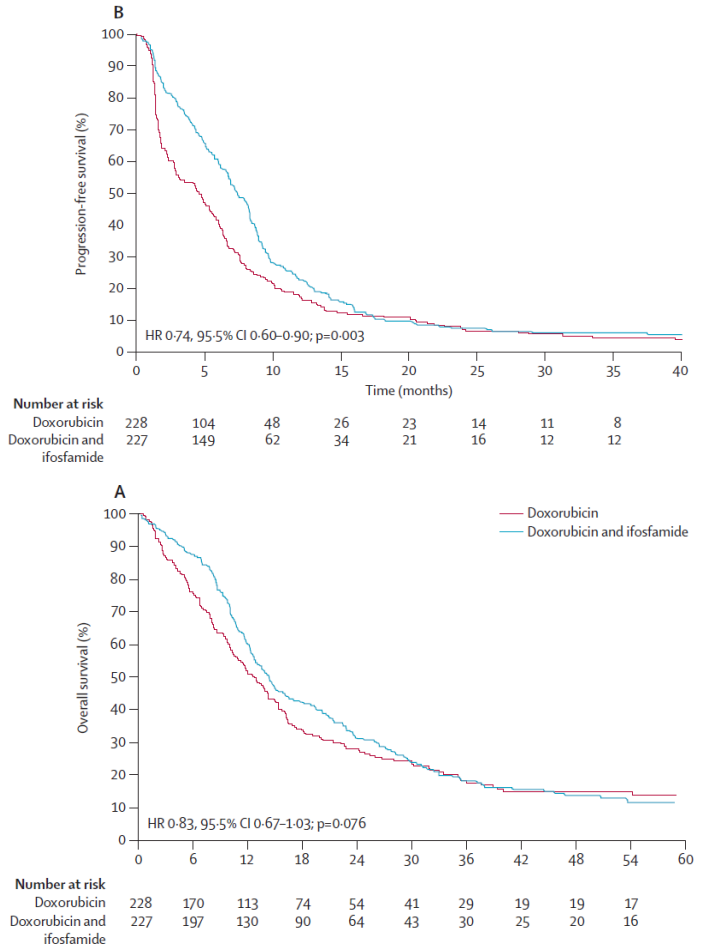


Fig 4. Overall survival.

2014[2]



Dox RR=14%
Dox + Ifos RR=27%

***Board Hint: Ifosfamide toxicities and countermeasures**
Hemorrhagic cystitis: Mesna
Neurotoxicity: Methylene Blue

1) Santoro 1995. JCO 13:1537
2) Judson 2014. Lancet 15:415

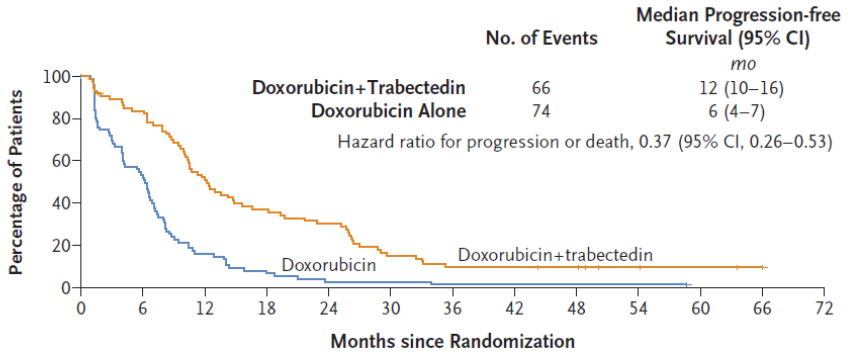
DRUG	MECHANISM	PHASE II SOFT TISSUE SARCOMA				PHASE III SOFT TISSUE SARCOMA			
		Primary Endpoint	Dox	Dox+D	Positive Trial?	Primary endpoint	Dox	Dox+D	Positive Trial?
Olaratumab	PDGFR-α mAb	PFS	4.1m (OS 14.7m)	6.6m (**OS 26.5m)**	No P=0.06	OS	19.7m	20.4m	No P=0.69
Palifosfamide	"New and Improved Ifosfamide"	PFS	4.4m	7.8m	Yes P=0.02	PFS	5.2m (OS 16.9m)	6.0m (OS 15.9m)	No P=0.16
Evofosfamide	Hypoxia-activated prodrug	PFS	N/A	6.5 m **(OS 21.5m)**	Yes (vs. historic)	OS	19.0m	18.4m	No P=0.53 (PFS yes)
Trabectedin	Novel alkylating agent	6-m PFS	N/A	58%	Yes (vs. historic)	PFS (OS) (LMS)	6.2m 24 m	12.2m 33 m	**Yes PFS, OS, ORR**

Blay 2008. Clin Cancer Res 14:6656.
Sessa 2009. Eur J Cancer 45:1153.
Verschraegen 2010. JCO 28 (15S): Abstract#10004.

Tap 2020 JAMA 323:1266
Chawla 2014. JCO 32:3299
Tap 2017. Lancet Oncol 18:1089
Tap 2016. Lancet 388:488
Ryan 2016. JCO 34:3898
Pautier 2022. Lancet Oncol 23:1044
Pautier 2024. NEJM 391:9

Doxorubicin/Trabectedin with Trabectedin Maintenance in Lyomyosarcoma

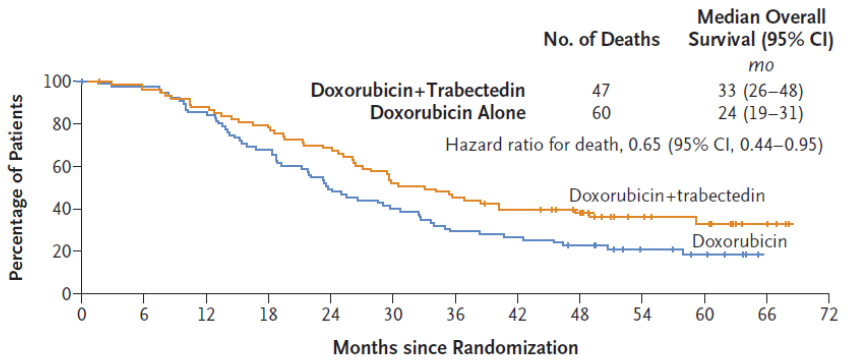
Progression-Free Survival



No. at Risk (censored data)

Doxorubicin+trabectedin	74 (0)	61 (1)	37 (1)	27 (1)	22 (1)	11 (1)	7 (1)	7 (1)	6 (2)	3 (5)	2 (6)	1 (7)	0 (8)
Doxorubicin alone	76 (0)	39 (1)	12 (1)	5 (1)	2 (1)	2 (1)	1 (1)	1 (1)	1 (1)	1 (1)	0 (2)		

Overall Survival



No. at Risk (censored data)

Doxorubicin+trabectedin	74 (0)	70 (1)	64 (1)	57 (1)	50 (1)	38 (1)	33 (1)	28 (2)	23 (6)	13 (15)	10 (17)	4 (23)	0 (27)
Doxorubicin alone	76 (0)	73 (1)	64 (1)	51 (1)	37 (1)	30 (1)	22 (1)	20 (1)	16 (2)	10 (7)	5 (11)	0 (16)	

	Dox/Trabectedin	Dox	p
Objective Response Rate	36% (27/71; 3 CR, 24 PR)	13% (19/76; 10 PR)	0.009
G3-4 AE	97%	56%	<0.001

Pautier 2022. Lancet Oncol 23:1044
Pautier 2024. NEJM 391:9

Doxorubicin-Based Soft Tissue Sarcoma Therapy

- ***1995***
  - "In advanced soft tissue sarcomas of adults, **single-agent doxorubicin is still the standard chemotherapy** against which more intensive or new drug treatments should be compared."[1]
- ***2014***
  - "If the goal of [STS] treatment is disease control, **doxorubicin alone remains an appropriate treatment**, but combination treatment can be justified if tumor shrinkage is desired, either to relieve symptoms or before another intervention."[2]
- ***2024***
  - "The trial results **support the use of doxorubicin plus trabectedin** for the first-line treatment of advanced or metastatic leiomyosarcomas, offering hope for improved outcomes in this challenging disease area."[3,4]

1) Santoro 1995. JCO 13:1537
2) Judson 2014. Lancet 15:422
3) Pautier 2022. Lancet Oncol 23:1044
4) Pautier 2024. NEJM 391:9

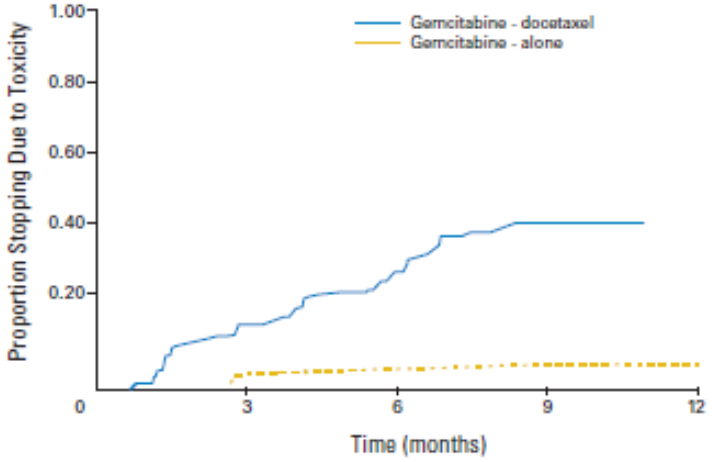
Sarcoma Systemic Therapy: Second-Line and Beyond

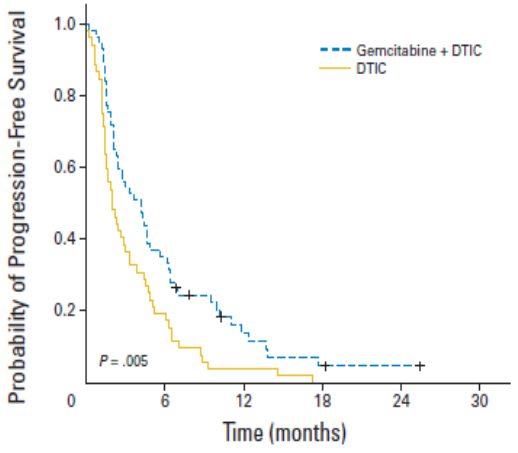
1) Maki,2007. JCO 25: 2755
2) Garcia-del-Muro, 2011. JCO 29: 2528

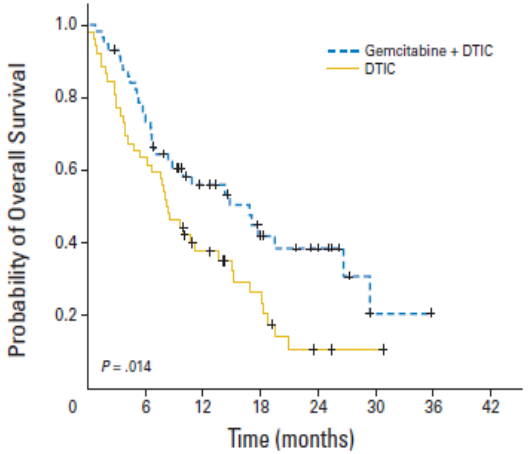
Gemcitabine-Based Therapy

- +Docetaxel[1]
  - vs. Gemcitabine
  - Adaptive Randomization
  - Median OS
    - 11.5 vs. 17.9m
  - Probability Comb>Gem=97%

- +Dacarbazine[2]
  - vs. Dacarbazine
  - Median OS
    - 7.8 vs. 18.3 m
  - Median PFS
    - 2.1 vs. 4.9 m







Doxorubicin versus Gemcitabine/Docetaxel(GT)

- Treatment-naïve STS
  - Dox 75mg/m2
  - Gem/Tax 675/75mg/m2
- Primary: PFR at 24 wk.
  - 27% uterine Leio
  - 4% Synovial
  - 12% Pleomorphic
  - 56% Other
- 257 pts randomized

"Dox was less toxic and easier to deliver than [GemTax], and should remain standard first-line treatment for locally advanced/metastatic STS."

- PFR@24w: 46%
- HR=1.28 favored Doxorubicin (p=NS)
- Median PFS
  - 23 w D vs.24 w GT
- RR
  - 66% D vs. 59% GT
- Median OS
  - 71w D vs. 63 w. GT

Seddon, 2015. JCO 33(suppl): Abs.#10500

Trabectedin

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

Trabectedin

- L-sarcomas[1]
- After anthracycline
- Primary: PFS
- *No OS benefit as monotherapy*
- Approved in Europe/US
  - Lipo- and Leiomyosarcomas
  - Unable to show benefit over DOX[2,3]
  - Esp. myxoid liposarcoma[4]
  - Dox/Trabectedin combination in Leio.[5,6]

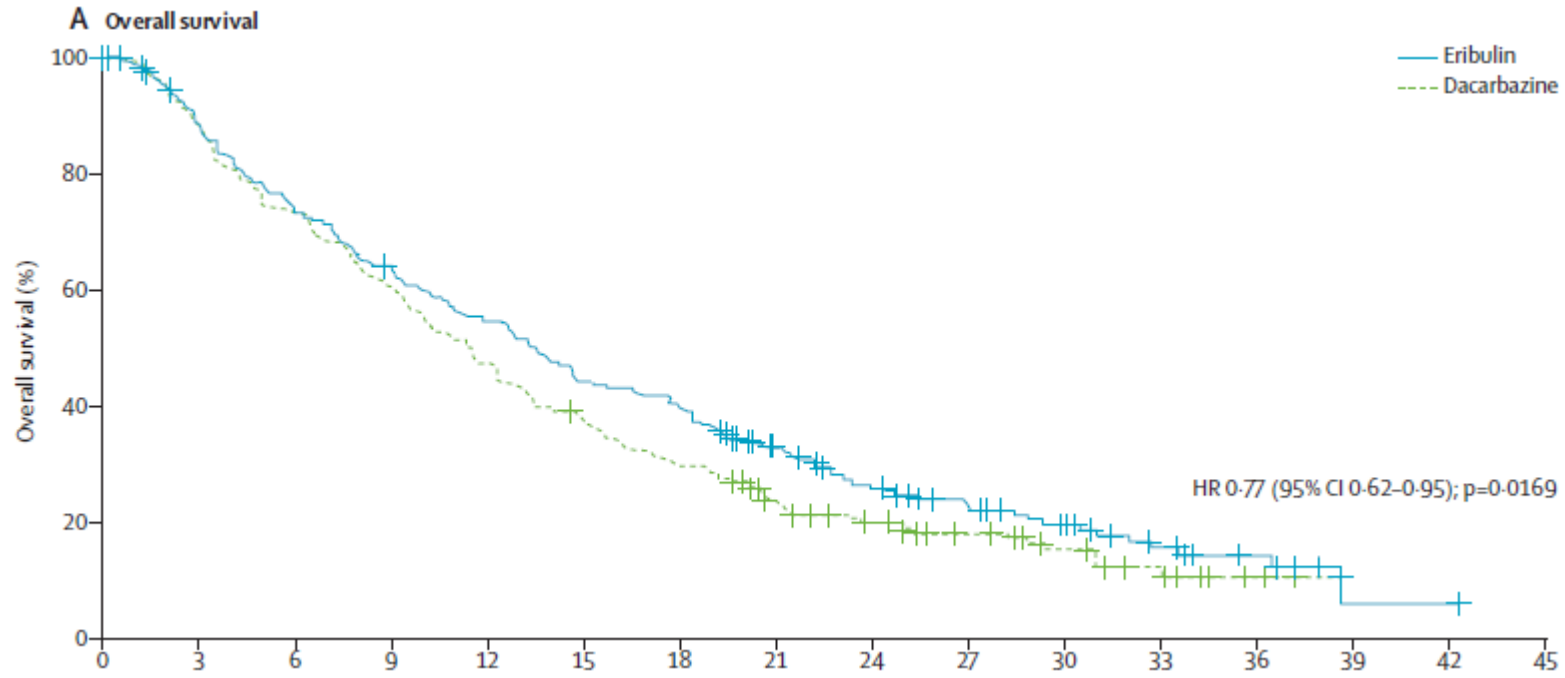
Table 4: Efficacy Results for Trial 1

Efficacy endpoint	YONDELIS N=345	Dacarbazine N=173
Progression-free survival		
PFS Events, n (%)	217 (63%)	112 (65%)
Disease progression	204	109
Death	13	3
Median (95% CI) (months)	4.2 (3.0, 4.8)	1.5 (1.5, 2.6)
HR (95% CI)[a]	0.55 (0.44, 0.70)	
p-value[b]	<0.001	
Overall survival[c]		
Events, n (%)	258 (67%)	123 (64%)
Median (95% CI) (months)	13.7 (12.2, 16.0)	13.1 (9.1, 16.2)
HR (95% CI)[a]	0.93 (0.75, 1.15)	
p-value[b]	0.49	
Objective Response Rate (ORR: CR+PR)		
Number of patients (%)	23 (7%)	10 (6%)
95% CI[d]	(4.3, 9.8)	(2.8, 10.4)
Duration of Response (CR+ PR)		
Median (95% CI) (months)	6.9 (4.5, 7.6)	4.2 (2.9, NE)

1) Yondelis Package Insert, Oct., 2015
2) Blay, 2014. Eur J Cancer 50:1137
3) Bui-Nguyen, 2015. Eur J Cancer 51: 1312
4) Dossi, 2015. Int J Cancer 136: 721
5) Pautier 2022. Lancet Oncol 23:1044
6) Pautier 2023. NEJM 391:9

Eribulin

- Novel tubulin inhibitor: G2/M cell cycle block
- Phase III L-sarcomas
- Eribulin (n=228) vs. dacarbazine (n=224)
- Primary endpoint: OS



Schoffski, 2016. Lancet 387:1629

Eribulin

Group	n	HR for OS	mOS vs Dacarbazine
All	452	0.77 (0.62-0.95)	13.5 vs 11.5
Liposarcoma	143	0.51* (0.35-0.75)	15.6 vs 8.4
Leiomyosarcoma	309	0.93 (0.71-1.20)	12.7 vs 13.0

- "…however, this study was not powered to draw definitive conclusions from such subgroup analyses."
- Approved in US for
  - "Unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen." -US Eribulin Package Insert 10/2016

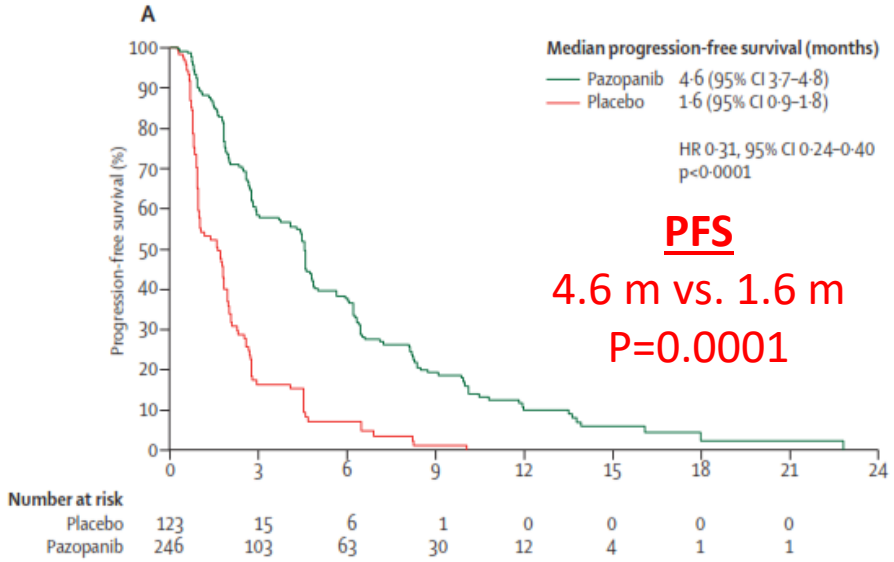
Schoffski, 2016. Lancet 387:1629

Targeted Therapy in Sarcomas

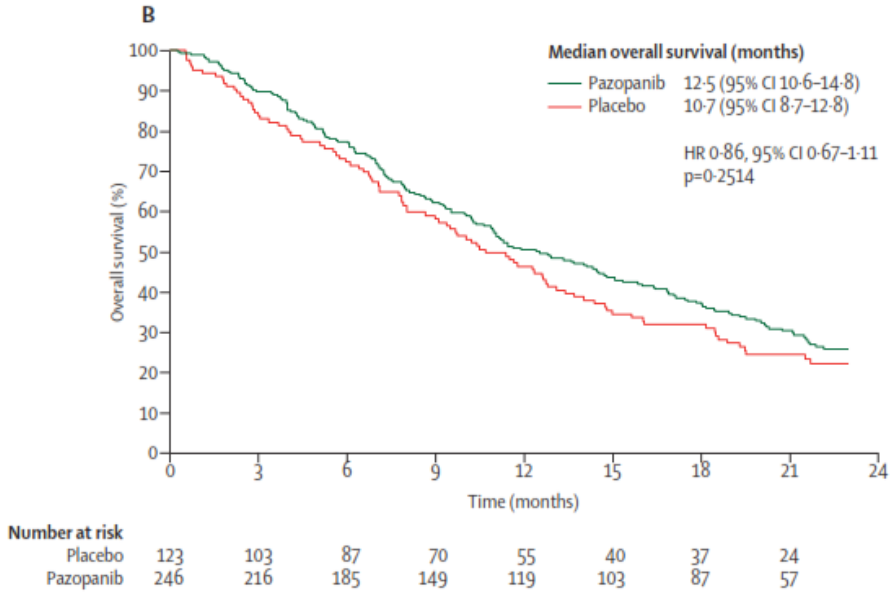
- Opportunities abound for targeted therapies in sarcomas
  - Fusion protein-driven sarcomas (~30%)
  - Less viable in sarcomas with complex pathogenetic mechanisms (~70%)
- Recurrent pathogenetic mechanisms!
  - Existing therapies may be applicable to specific diseases
    - Imatinib: Chronic myelogenous leukemia/Gastrointestinal stromal tumors
    - Denosumab: Osteoporosis/Giant cell tumor of bone
    - Anti-Angiogenic TKI's
      - Cediranib/Others: Alveolar Soft Part Sarcoma
      - Sorafenib/Pazopanib: Desmoid tumors, chordomas
  - More specific biological understanding: more effective/less broadly applicable
    - Pexidartinib: CSF1R inhibitor in Tenosynovial Giant Cell Tumor
  - Less specific understanding: less effective/more broadly applicable

Pazopanib

- Anti-angiogenic tyrosine kinase inhibitor
- 1-4 prior therapies
- vs. Placebo
- Primary: 6-m PFS
- ORR:
  - 0% placebo
  - 6% pazopanib
- Approved for STS
  - (**BOARD Hint: except liposarcomas**)



PFS
4.6 m vs. 1.6 m
P=0.0001

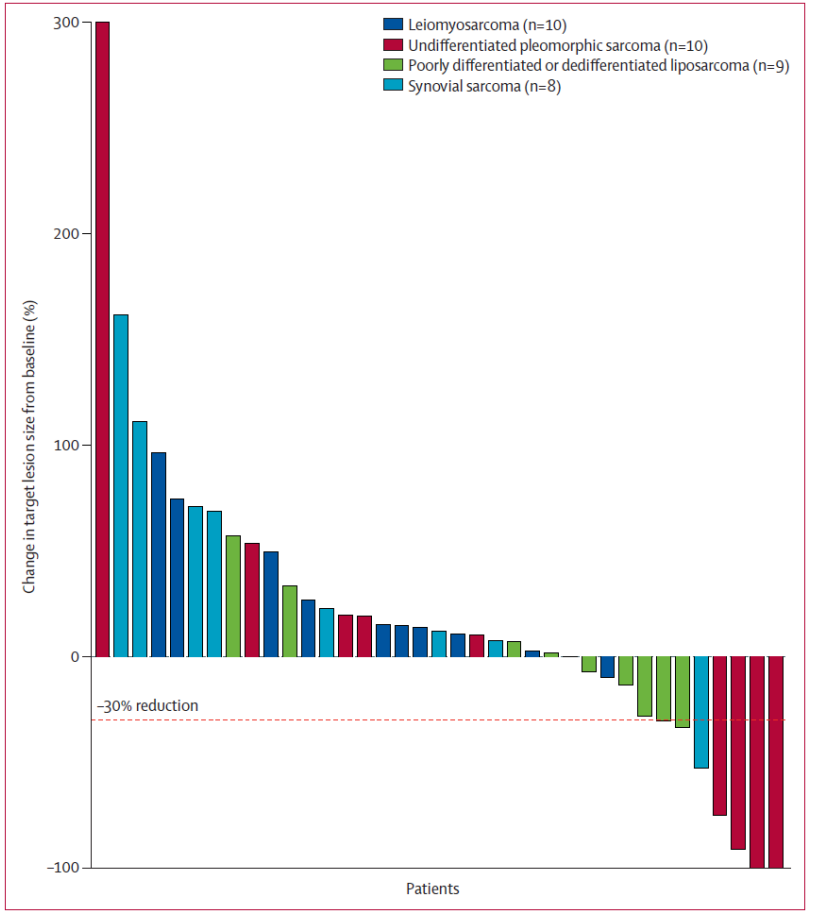


Van der Graff, 2012. Lancet 379: 1879

Immunotherapy of Sarcomas

- Major advances in immune treatment of cancer
- Several major mechanisms of immune evasion have been identified
- Sarcomas do not necessarily have factors associated with immune response
- Diversity of sarcomas is probably an issue
- May be especially important in sarcomas with less well understood biology
  - Undifferentiated pleomorphic sarcoma
  - Alveolar Soft Part Sarcoma
  - Myxofibrosarcoma
  - Angiosarcoma

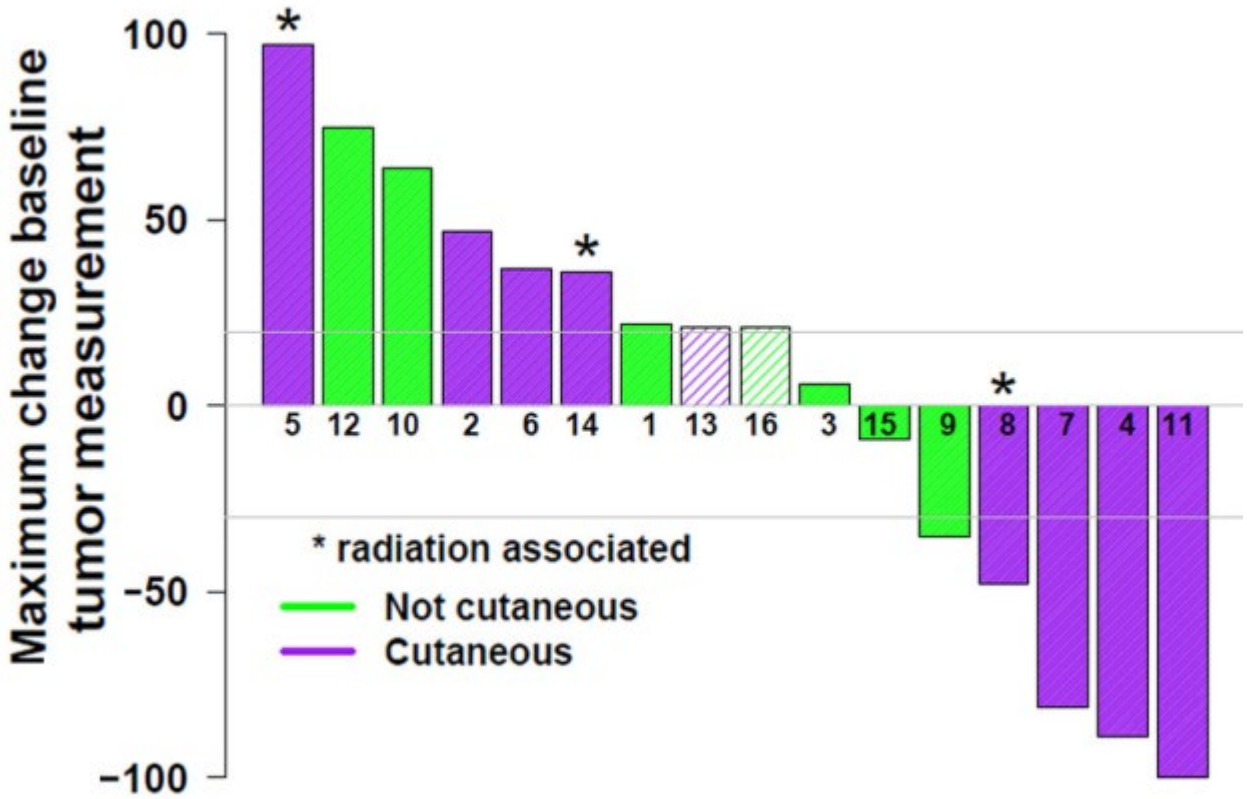
Pembrolizumab in Soft Tissue Sarcomas

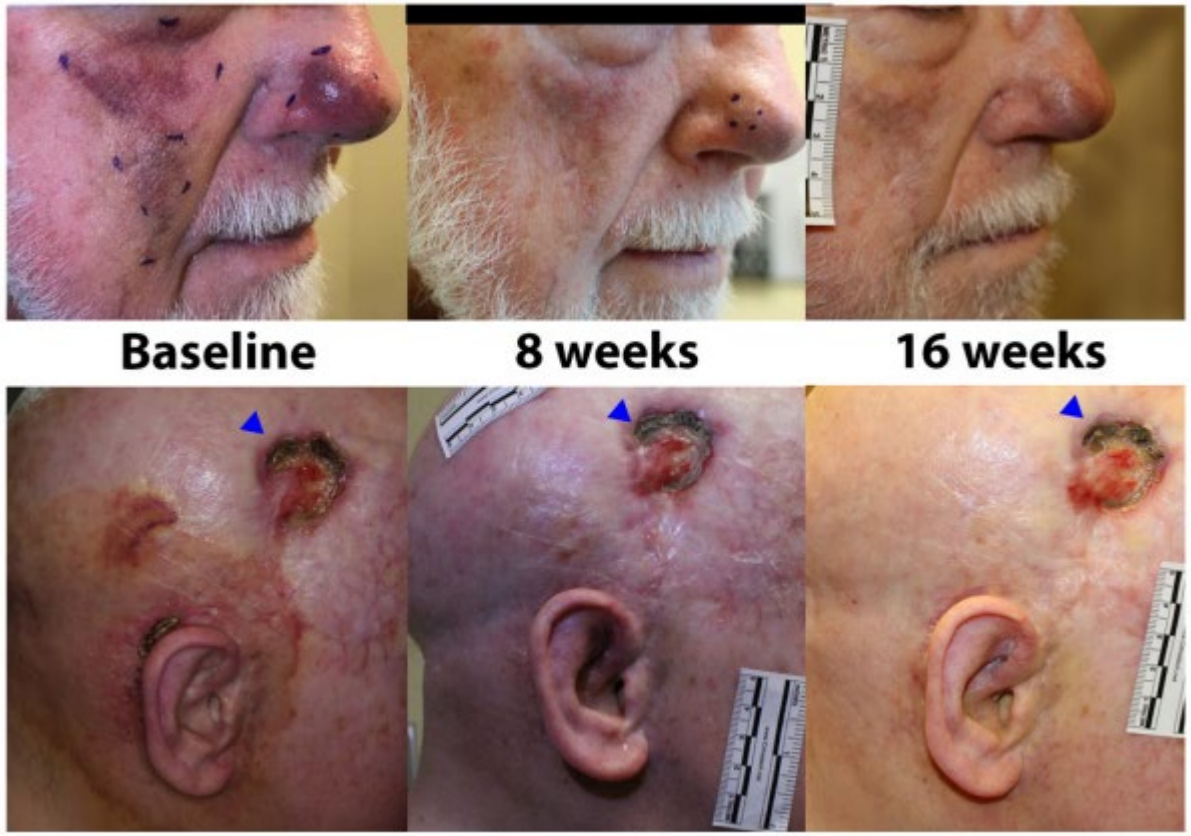


Tawbi 2017. Lancet Oncol. 18: 1493

Ipilimumab/Nivolumab in Angiosarcoma

- ~400 cases per year in US
- 5-year survival 30-40%, even if localized
- Different clinical presentations/scenarios
  - Face/Scalp: high mutational burden
  - Visceral
  - Radiation-associated (often antecedent breast cancer treatment)
- Case reports suggesting activity of checkpoint inhibitors.
- DART Study
  - Serial single-arm phase II screening studies.
  - Primary Endpoint: Objective Response Rate
  - 2-stage Design
  - Stage 1: At least one response out of 6 patients.
  - Stage II: 2 or more responses our of 16 total patients->merits further investigation.





Wagner 2021. JITC 9:e002990

Afamitresgene autoleucel in Synovial Sarcoma

- Autologous CAR-T against MAGE-A4 antigen
  - Expressed frequently in synovial sarcoma (also myxoid round cell liposarcoma)
- HLA-A-02-restricted
- SS with progression after doxorubicin or ifosfamide
- Primary endpoint ORR
- Cytokine Release Syndrome
  - 75% Any Grade
  - 2% >Grade 2
- Immune Effector Cell-associated Neurotoxicity: Grade 1 2% (n=1)

Table 4. Efficacy Results* for SPEARHEAD-1 (Cohort 1)

Endpoint	**TECELRA Treated Population** **N=44**
Overall Response Rate	43.2%
(95% CI)[1]	(28.4, 59.0)
Complete response rate, n (%)	2 (4.5%)
Partial response rate, n (%)	17 (38.6%)
Median Duration of Response# in months	6.0
(95% CI)[2]	(4.6, NR)
Min, Max	1.9, 36.1+
Patients with DoR ≥ 6 months, %[2]	45.6%
Patients with DoR ≥ 12 months, %[2]	39.0%

Afamitresgene autoleucel package insert: available at www.tecelra.com

Gastrointestinal Stromal Tumors

Gastrointestinal Stromal Tumors (GIST)

- Tumors arising from Interstitial Cells of Cajal
- From esophagus to anus
- c-KIT/CD117 mutations are characteristic
  - Leads to constitutive activation of tyrosine kinase
- Another marker is DOG1 (a calcium channel seen on GIST cells)-more specific than c-KIT

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.

Fletcher et al, Human Path 2002

Medical Management: Targeting GIST Biology

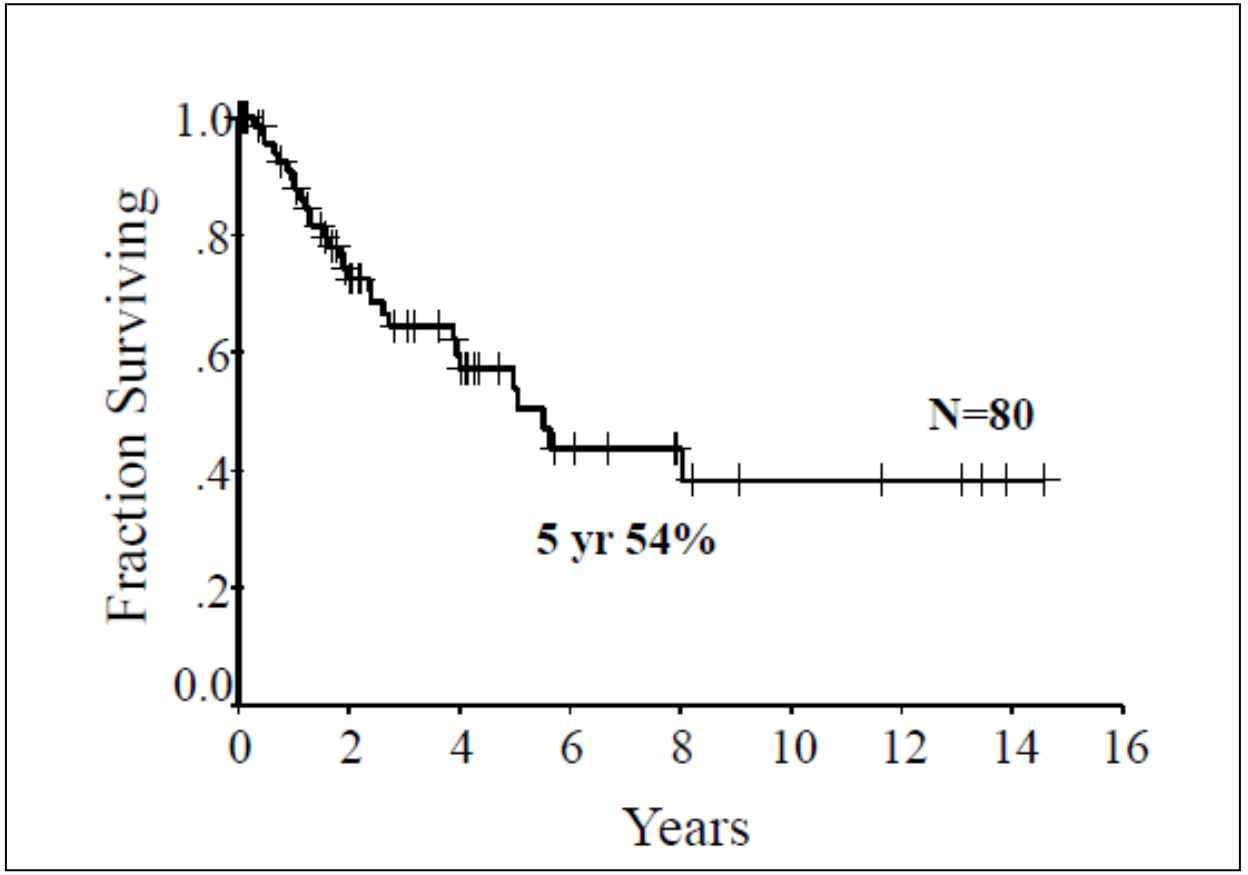
- Mutations in GIST- *these are different from IHC and can only be detected by PCR or other sequencing based methods*
  - KIT (~80%)- *NOTE: KIT expression by IHC is not the same as having a KIT mutation*
    - *Exon 11- most common, 400 mg imatinib*
    - *Exon 9- often in small bowel, 800 mg imatinib*
  - 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→ may take a long time (many months) before enough tumor shrinkage to get to surgery
- Rarely radiation
- Radiofrequency ablation (RFA), embolization, or chemoembolization

Historic Surgical Outcomes

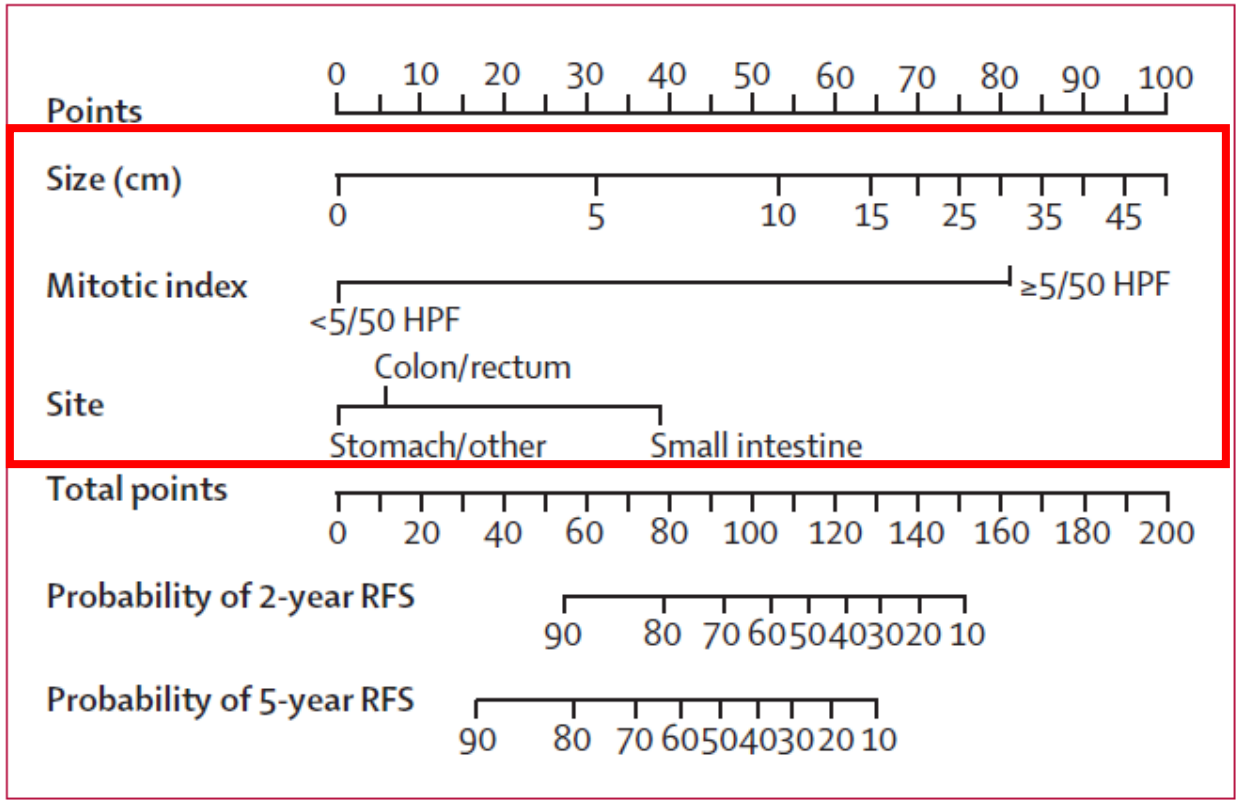
- 50% of patients can recur postoperatively, usually in the liver or peritoneum, and will die within 5 years **without additional treatment**



DeMatteo, *Ann Surg,* 2000.

Predicting Postop Recurrence

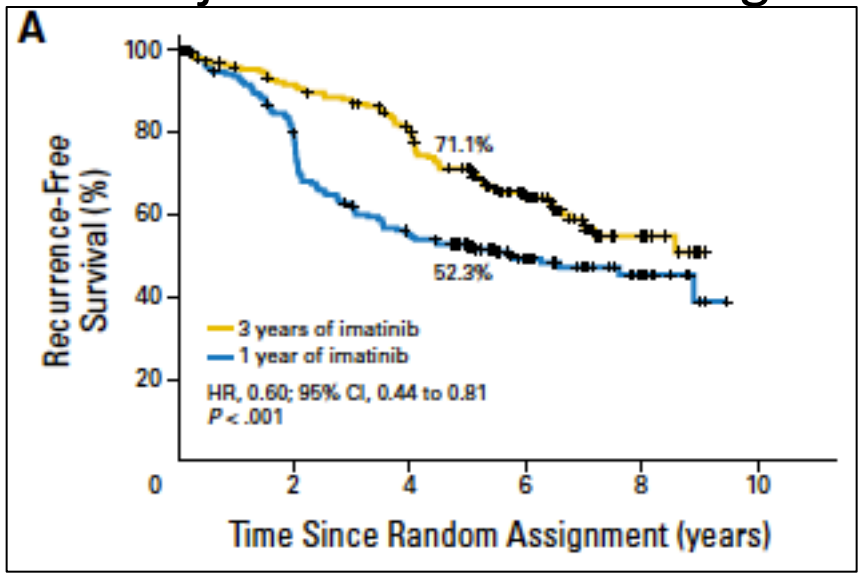
- **Who needs medicine after surgery?**

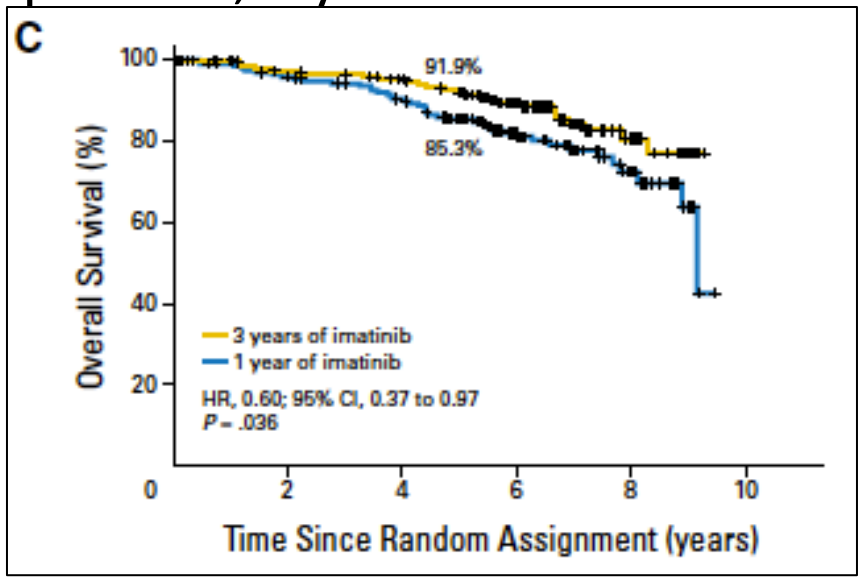


https://www.mskcc.org/nomograms/gastrointestinal

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

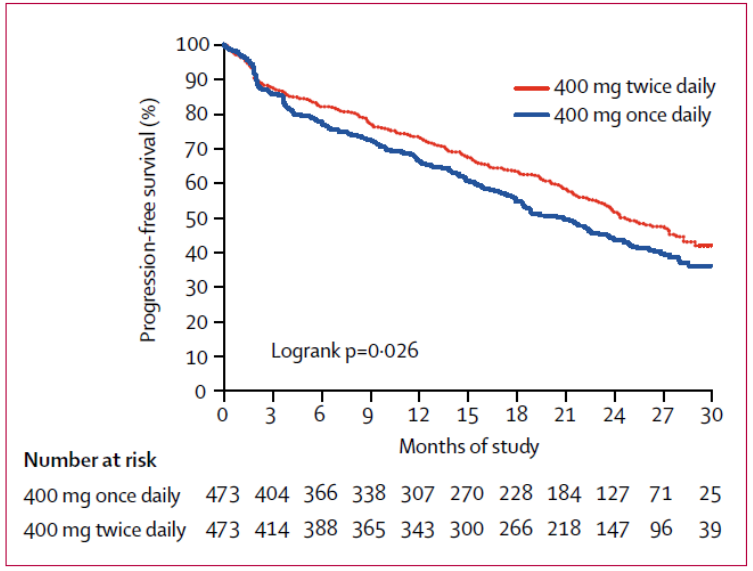
Medical Management: GIST Metastatic Disease

- **Imatinib (or Avapritinib/D842V) → Sunitinib → Regorafenib → Ripretinib → Clinical Trial**

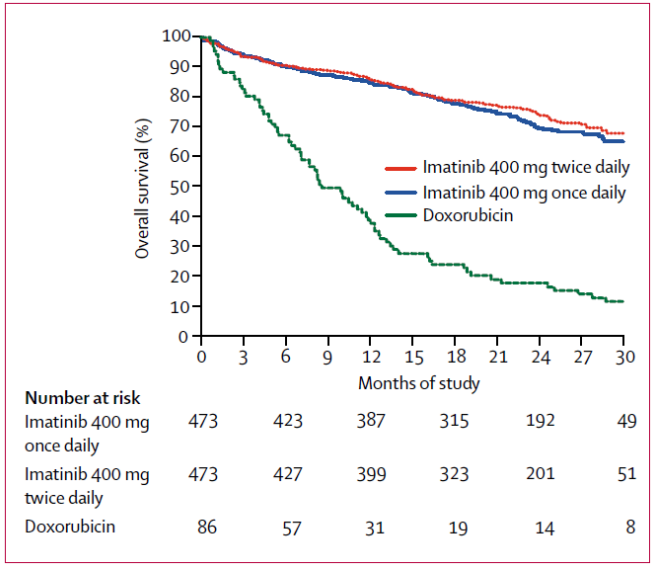
Medical Management: Metastatic Disease

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

1°: Progression-free Survival



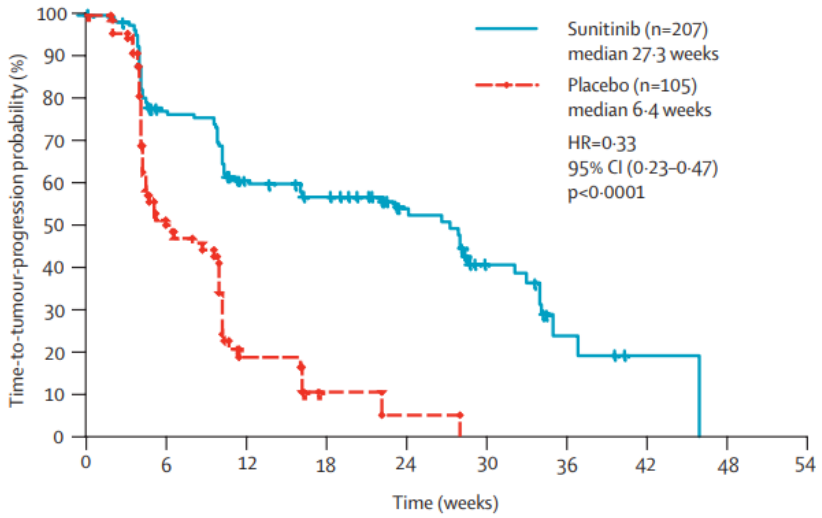
2°: Overall Survival

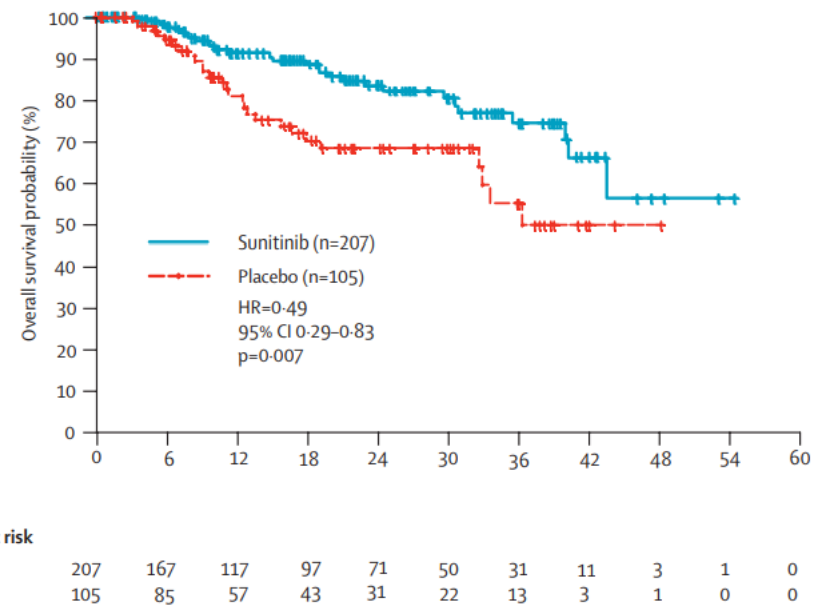


Verweij *et al.* Lancet 2004, 364. 1127-34.

Medical Management: 2nd Line Metastatic Disease

- 2nd line: sunitinib (Demetri 2006)





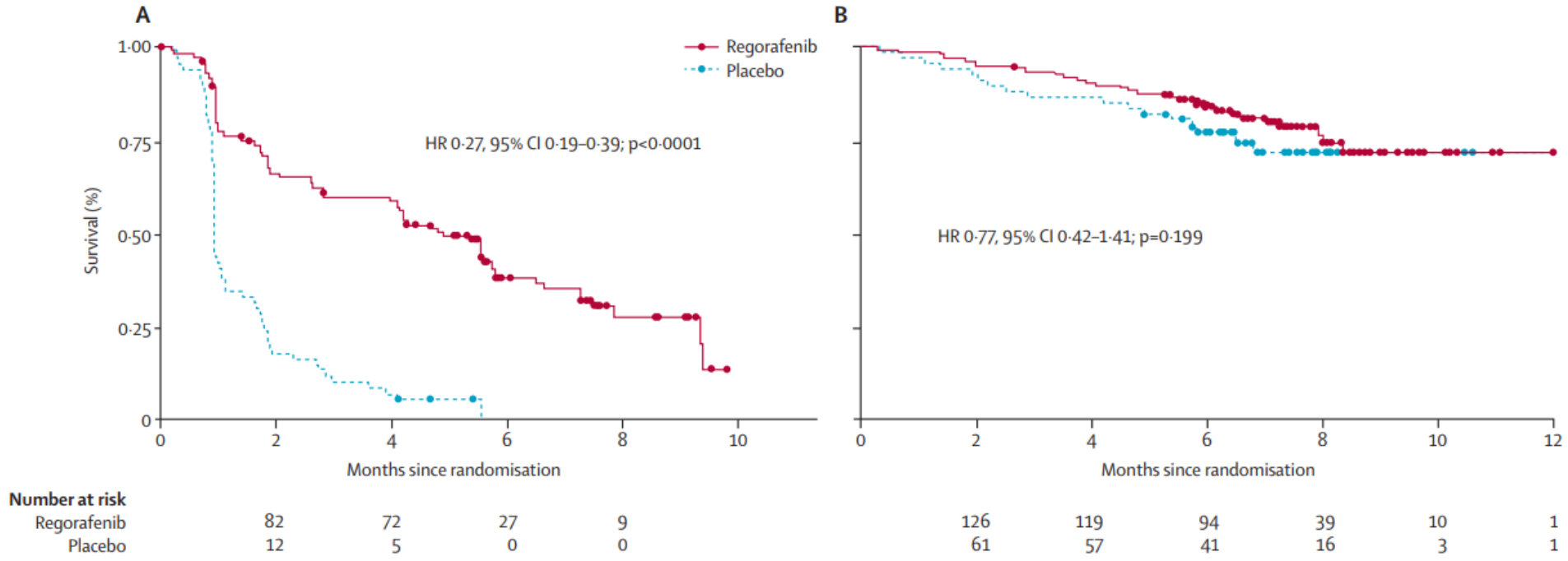
Improved Progression Free Survival

Improved Overall Survival

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

Medical Management: 3rd Line Metastatic Disease

- 3rd line: Regorafenib (Demetri 2013)



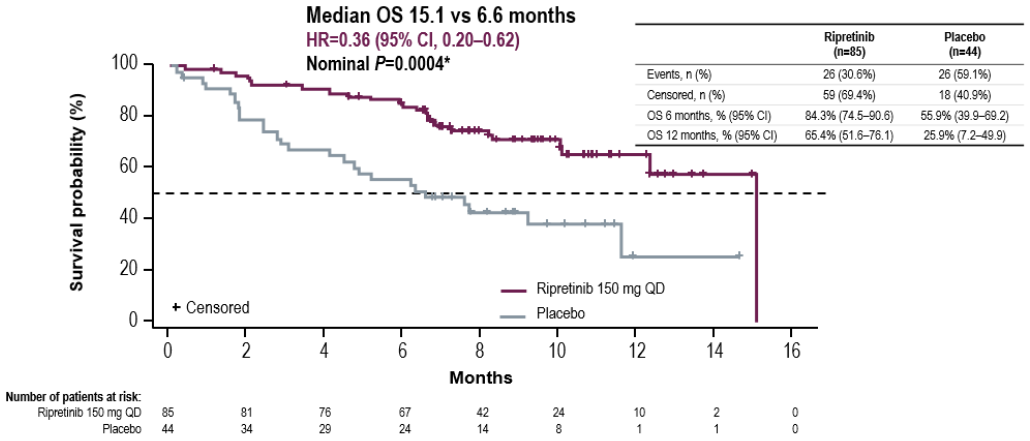
Improved Progression Free Survival

Trend Improved Overall Survival

Medical Management: GIST Metastatic Disease

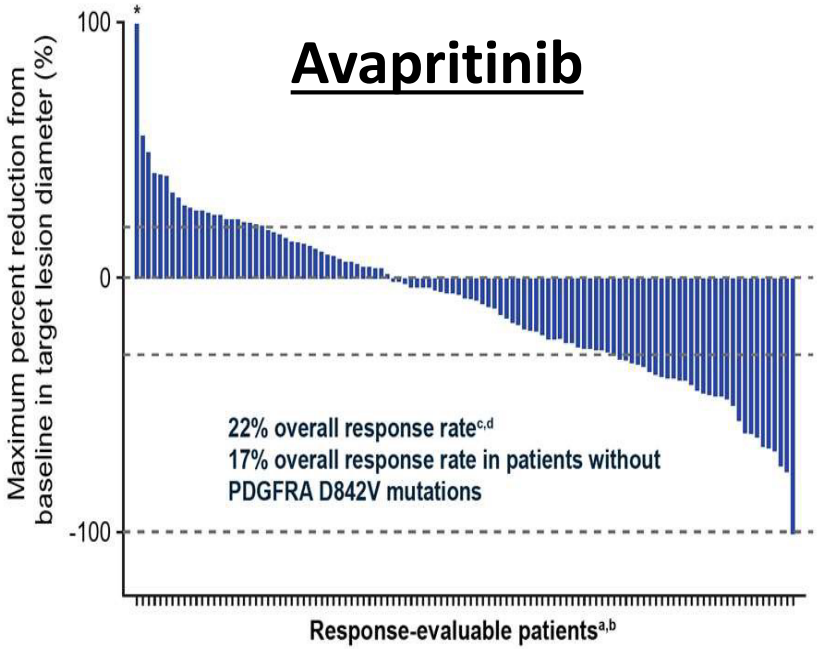
- **4th Line and beyond (Ripretinib recently approved)**

Ripretinib



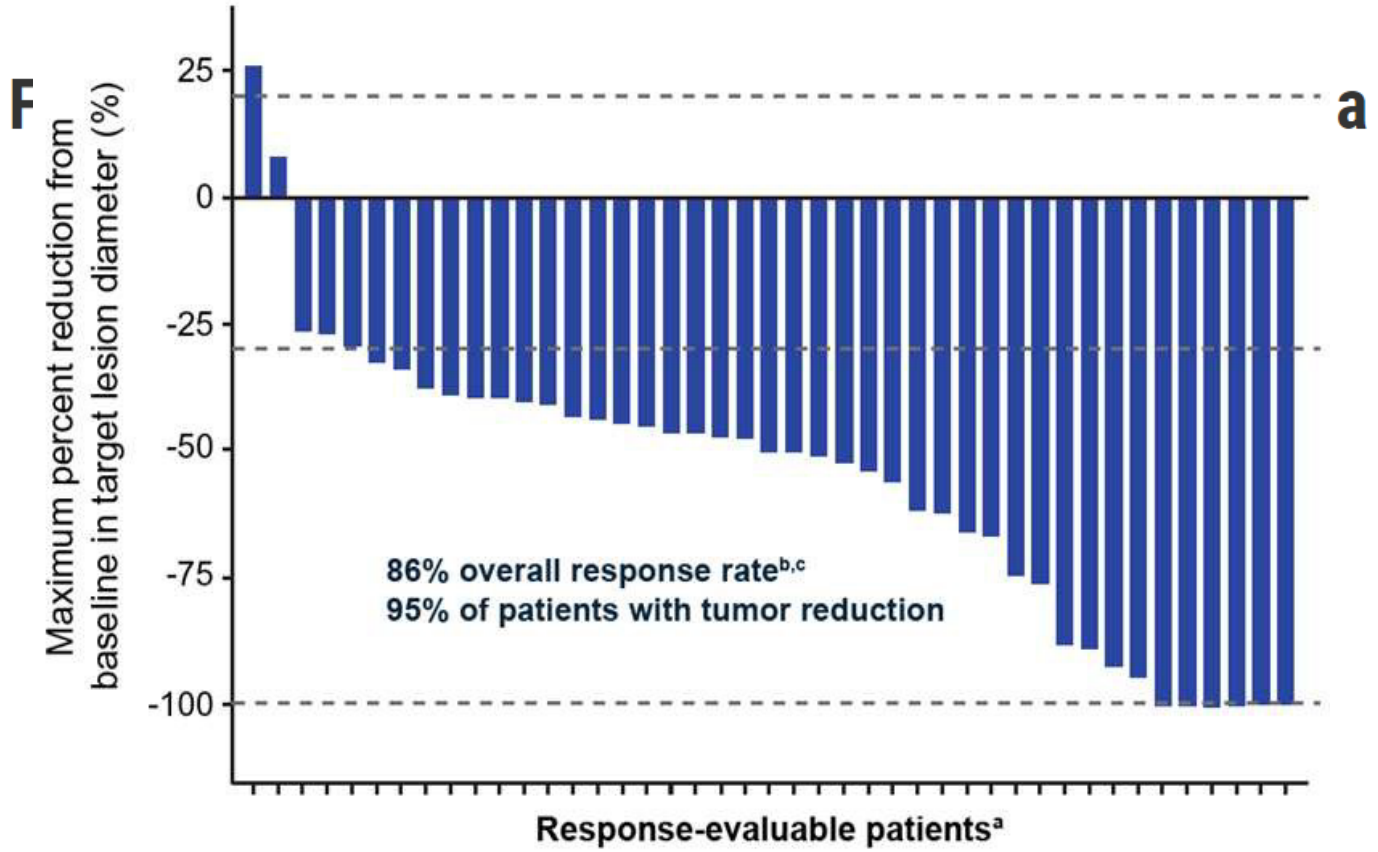
	Ripretinib (n=85)	Placebo (n=44)
Events, n (%)	26 (30.6%)	26 (59.1%)
Censored, n (%)	59 (69.4%)	18 (40.9%)
OS 6 months, % (95% CI)	84.3% (74.5–90.6)	55.9% (39.9–69.2)
OS 12 months, % (95% CI)	65.4% (51.6–76.1)	25.9% (7.2–49.9)

Avapritinib



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

Medical Management: GIST Metastatic Disease



growing.

- **Avapritinib in PDGFRA exon 18 mutant GIST (D842V)**

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

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

- **Angiosarcoma- responsive to taxanes
- Dermatofibrosarcoma Protuberans (DFSP)- imatinib
- Pigmented Villonodular Tenosynovitis/Tenosynovial Giant Cell Tumor- Pexidartinib (CSF1R inhibition)
- **Desmoid- nirogacestat (gamma-secretase inhibitor), sorafenib, imatinib. (associated with Familial Adenomatous Polyposis)
- Giant Cell Tumor of Bone- denosumab
- Inflammatory myofibroblastic tumor (IMT)- if ALK positive, can respond to ALK inhibitors
- Epithelioid Sarcoma-EZH2 methyltransferase inhibitor Tazemetostat
- PEComa- mTOR inhibitors (nab-sirolimus)
- Pediatric sarcomas in adults- aggressive multi-D care

Conclusions and the Future

- **Primary Therapy**
  - Surgery is still the primary therapy of sarcomas.
  - Radiotherapy improves local control.
  - Systemic therapy
    - Important in sarcomas of childhood.
    - Still developing role in other types of sarcomas.
- **Advanced Disease Therapy**
  - Doxorubicin-based therapy is **still** a backbone of treatment
    - Dox combination with trabectedin in Leio=OS benefit!
    - “One-size-fits-all” may not be the way to progress
    - Need to identify key aspects of mesenchymal biology
  - More recent progress based on biological understanding
- **Key to progress: Understanding BIOLOGY**
  - Biology of the disease (Targeted therapy)
  - Biology of the host (immunotherapy)
  - GIST Therapy