Stanford
Cancer Institute
A National Cancer Institute
Comprehensive Cancer Center

Stanford | MEDICINE

Soft Tissue Sarcomas

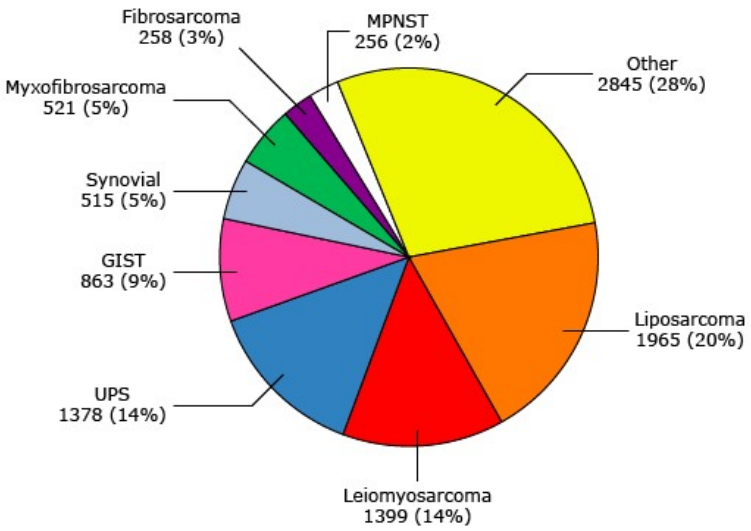
Nam Bui, MD

Clinical Assistant Professor

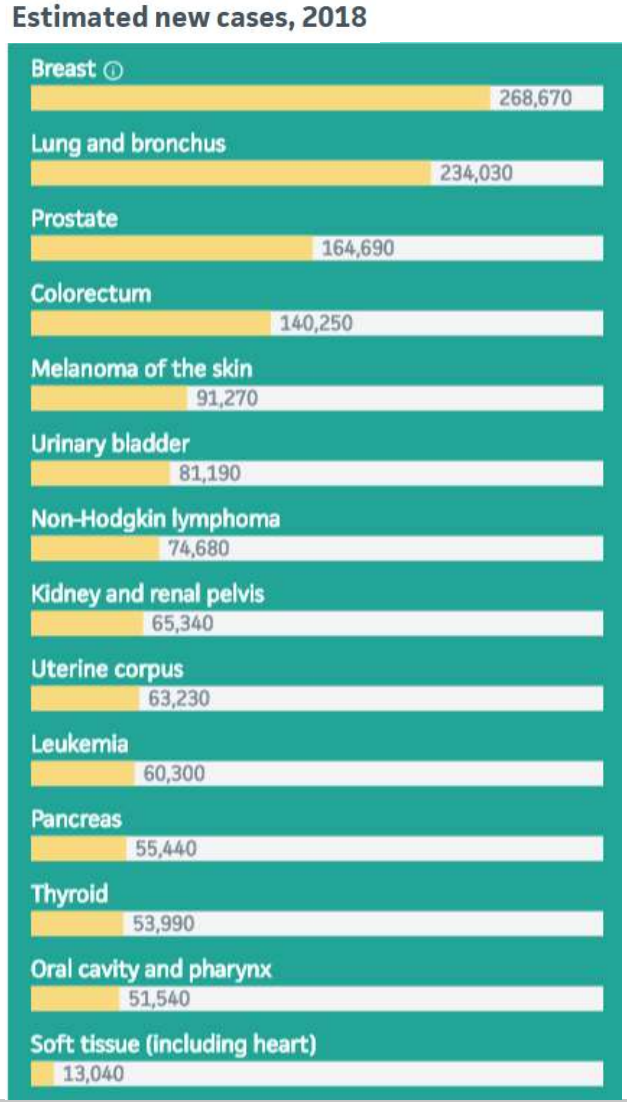
Sarcoma / Phase 1

Sarcoma Epidemiology

- Rare tumor with mesenchymal cell origin
- Over 100 different histologic subtypes



Management of Soft Tissue Sarcoma, General Description, 2nd ed, 2016, p. 7, Brennan M, Antonescu C, Alektiar K, Maki R



American Cancer Society 2018

Current Classification of Sarcomas

Vascular STS
- Angiosarcoma
- Hemangiosarcoma
- Lymphangiosarcoma
- Hemangioendothelioma
- Hemangiopericytoma
- Kaposi sarcoma

Neural STS
- Malignant peripheral nerve sheath tumor
- Malignant paraganglioma
- Neuroblastoma, neuroepithelioma
- Granular cell tumor

Adipose STS
- Atypical lipomatous tumor
- Myxoid/round cell liposarcoma
- Dedifferentiated liposarcoma

Pleomorphic STS
- Liposarcoma, malignant fibrous histiocytoma

Neuromuscular STS
- GIST

Unclassified

Smooth Muscle STS
- Gastrointestinal, genitourinary, cutaneous, vascular

Skeletal Muscle STS
- ARMS, ERMS, pleomorphic RMS

Fibrous STS
- Fibrosarcoma
- Fibromyxoid sarcomas
- Desmoid tumor
- Dermatofibrosarcoma
- Inflammatory myofibroblastic tumor

Unknown Tissue
- Synovial sarcoma
- Alveolar soft part sarcoma
- Epithelioid sarcoma

Bone Sarcomas
- Osteosarcoma (+ variants)
- Chondrosarcoma (+ variants)
- Giant cell tumor of bone
- Ewing sarcoma family of tumors

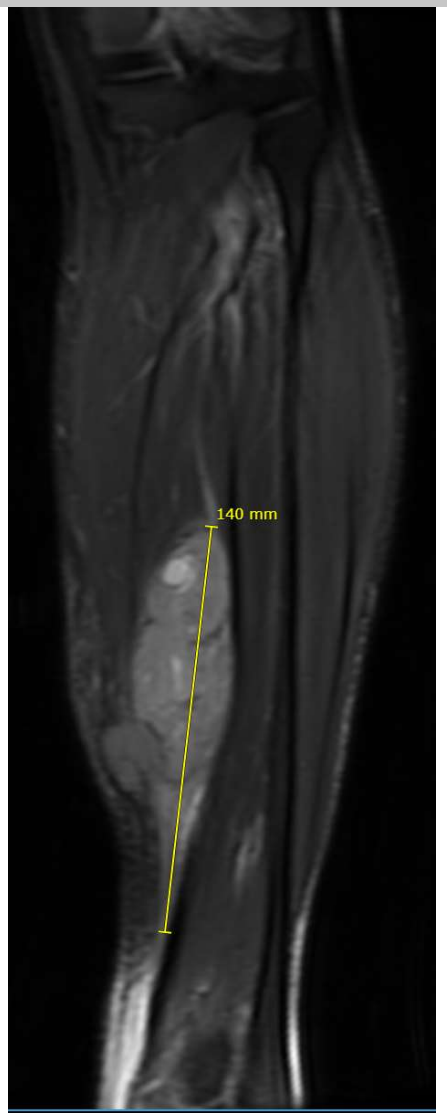
Extraskeletal Bone Sarcomas
- Osteosarcoma
- Ewing sarcoma family
- Chondrosarcoma

ARMS = alveolar rhabdomyosarcoma;
ERMS = embryonal rhabdomyosarcoma; RMS = rhabdomyosarcoma; STS = soft tissue sarcoma

https://www.medscape.org/viewarticle/748757_transcript

Case #1

- 58M presents to clinic with mass in his left leg.
- MRI shows 14cm mass in the anteromedial calf
- Biopsy shows high grade leiomyosarcoma
- Next steps?



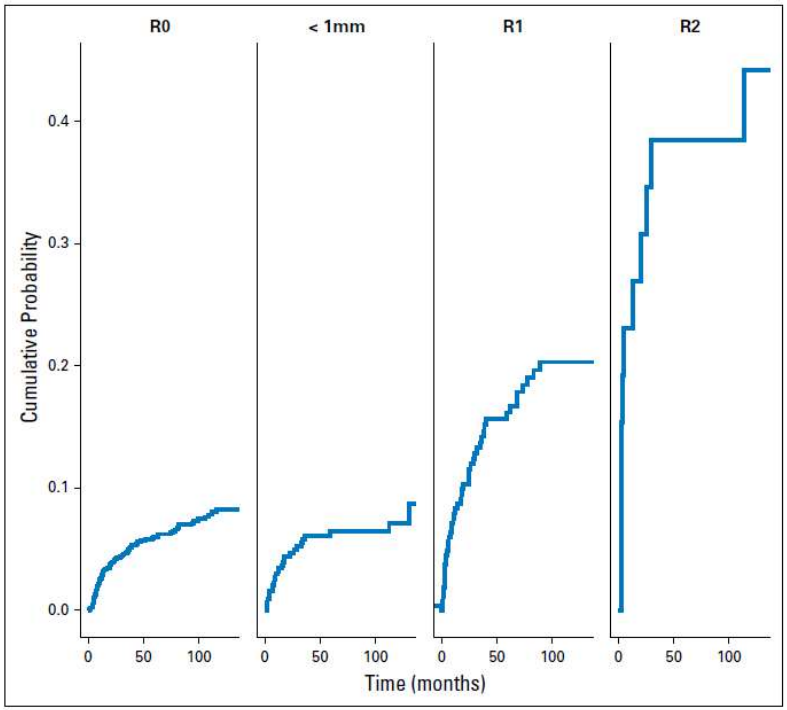
Staging

- Metastasis in sarcoma ranges from 10-50% depending on risk factors and is most often to the lung (>50%)
- Regional lymph node metastases are extremely rare (2.6% of patients)

- Staging scans generally include
  - CT Chest
  - PET/CT Whole Body

Localized Sarcoma

- **KEY:** Surgical resection with clear margins at an experienced sarcoma center
- Margin status is highly predictive of local recurrence



Gundle et al. JCO 2018

Controversy: Adjuvant Chemotherapy?

SMAC 1997 Meta-analysis (Doxorubicin)

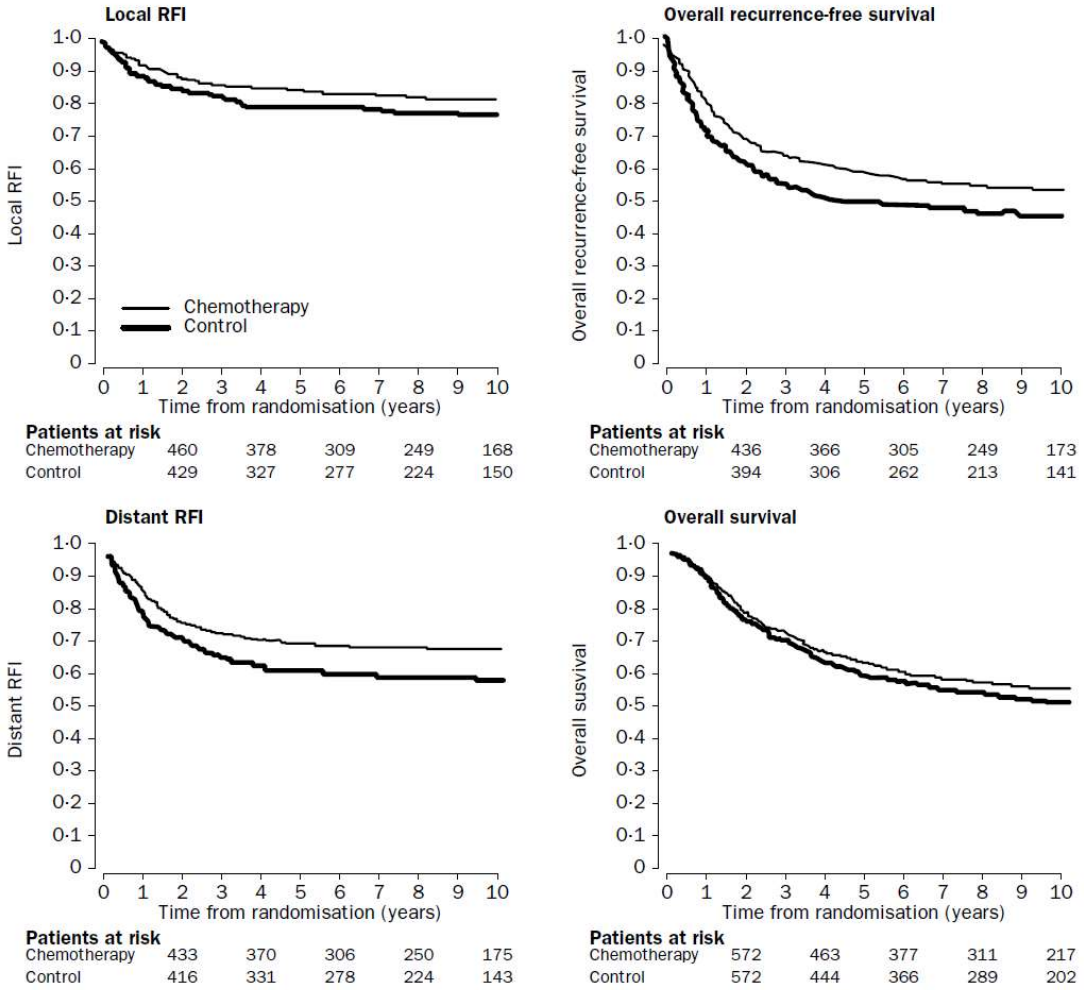


Figure 2: **Kaplan-Meier curves of local RFI, distant RFI, overall recurrence-free survival, and overall survival for adjuvant chemotherapy versus control**

Study	Accrual period	Drugs given in addition to doxorubicin	Doxorubicin dose (mg/m²)	
			Total	Per cycle
GOG[21]	1973–82	None	480	60
DFCI/MGH[22]	1978–83	None	450	90
ECOG[23]	1978–82	None	490	70
SSG[24]	1981–86	None	540	60
Rizzoli[25,26]	1981–86	None	450	75
IGSC[27,28]	1983–86	None	420	70
MDA[29]	1973–76	Cyclophosphamide, dactinomycin, vincristine	420	60
Mayo[30,31]	1975–81	Vincristine, cyclophosphamide, dactinomycin, dacarbazine	200	50
NCI 4[32,33]†	1977–81	Cyclophosphamide, methotrexate	500–550	50–70
NCI 5[34,35]†	1977–89	Cyclophosphamide, methotrexate	500–550	50–70
NCI 6[32,33]†‡	1977–81	Cyclophosphamide, methotrexate	500–550	50–70
EORTC[36]	1977–88	Cyclophosphamide, vincristine, dacarbazine	400	50
Bergonie[37]	1981–88	Cyclophosphamide, vincristine, dacarbazine	400–500	50
Sakk (57/87) (unpublished)	1987–90	Ifosfamide	550	50–90

SMAC. Lancet 1997

Updated 2008 Meta-analysis (AIM)

Pervaiz. Cancer 2008

TABLE 2
Relative Risks and 95% Confidence Intervals for Local Recurrence, Distant Recurrence, Overall Recurrence, and Survival

	Local recurrence		Distant recurrence		Overall recurrence		Survival	
Treatment	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Doxorubicin	0.75	0.56-1.01	0.69	0.56-0.86	0.69	0.56-0.86	0.84	0.68-1.03
Doxorubicin with ifosfamide	0.66	0.39-1.12	0.61	0.41-0.92	0.61	0.41-0.92	0.56	0.36-0.85
Combined	0.73	0.56-0.94	0.67	0.56-0.82	0.67	0.56-0.82	0.77	0.64-0.93

RR indicates relative risk, 95% CI, 95% confidence interval.

TABLE 3
Absolute Risk Reductions and 95% Confidence Intervals for Local Recurrence, Distant Recurrence, Overall Recurrence, and Survival

	Local recurrence		Distant recurrence		Overall recurrence		Survival	
Treatment	ARR	95% CI	ARR	95% CI	ARR	95% CI	ARR	95% CI
Doxorubicin	3%	1%-7%	9%	4%-14%	9%	4%-14%	5%	6%-21%
Doxorubicin with ifosfamide	5%	1%-12%	10%	1%-19%	12%	3%-21%	11%	3%-19%
Combined	4%	0%-7%	9%	5%-14%	10%	5%-15%	[illegible]	[illegible]

ARR indicates absolute risk reduction, 95% CI, 95% confidence interval.

Randomized Control Trial (EORTC 2012)

- 351 patients randomized to adjuvant AIM (± post-op XRT) vs no chemotherapy
- Included G2 sarcoma, slightly lower ifosfamide dose (5 g/m2)

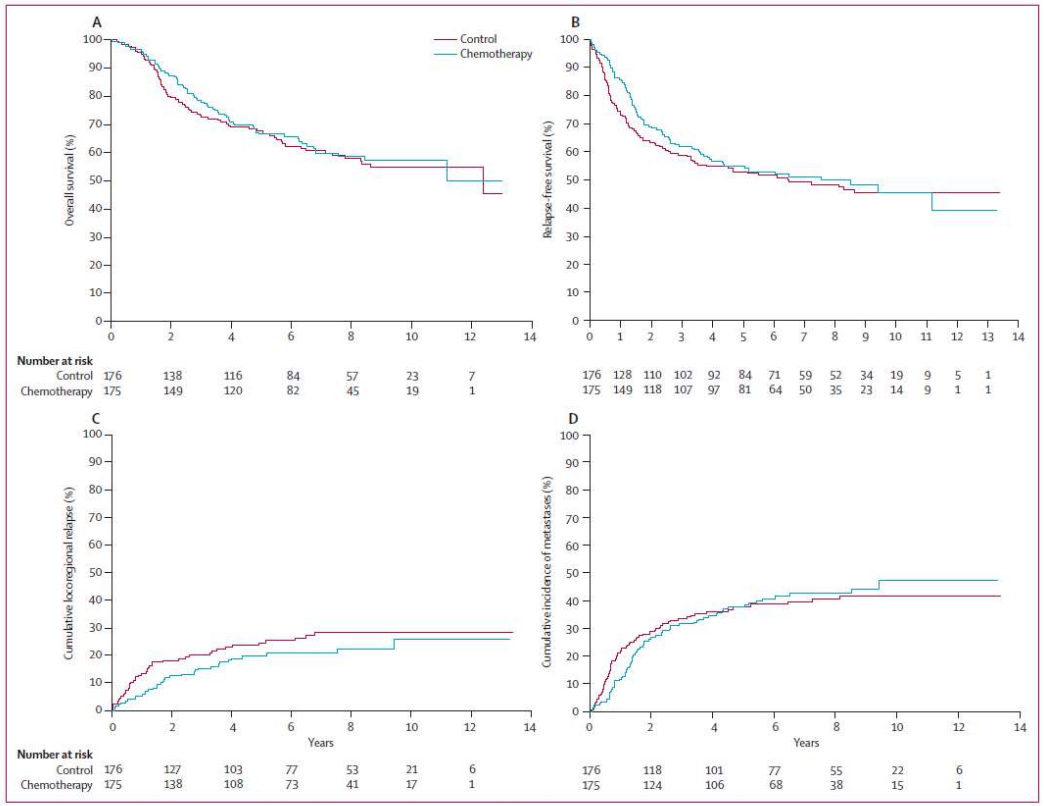


Figure 2: **Survival and relapse rates for patients randomly assigned to control or adjuvant chemotherapy**
(A) Overall survival in the intention-to-treat population. The number of observed events was 73 in the control group and 68 in the chemotherapy group. (B) Relapse-free survival in the intention-to-treat population. The number of observed events was 91 in the control group and 87 in the chemotherapy group. (C) Cumulative locoregional relapse rate. The number of observed events was 44 in the control group and 34 in the chemotherapy group. (D) Cumulative metastatic relapse rate. The number of observed events was 69 in the control group and 72 in the chemotherapy group.

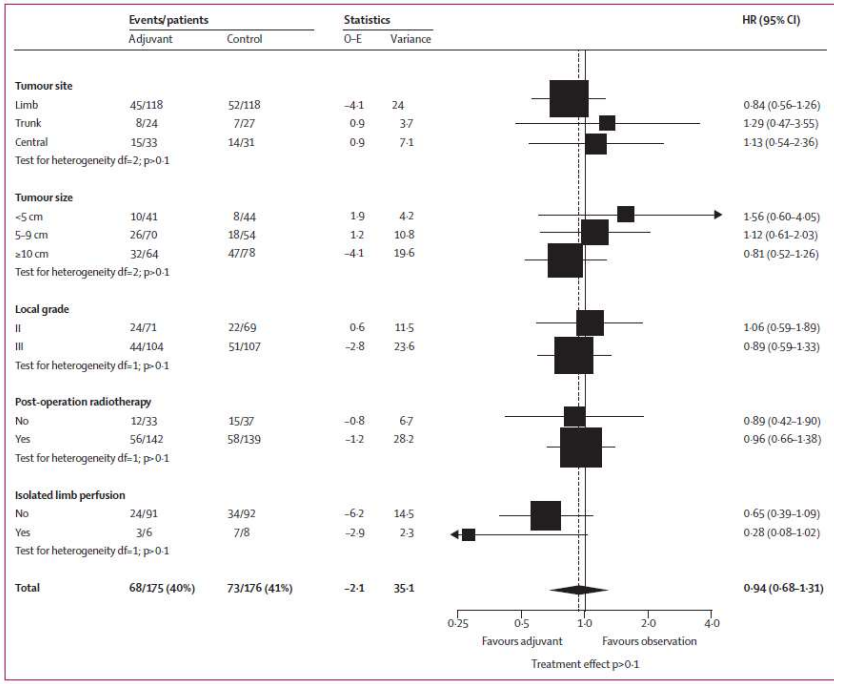
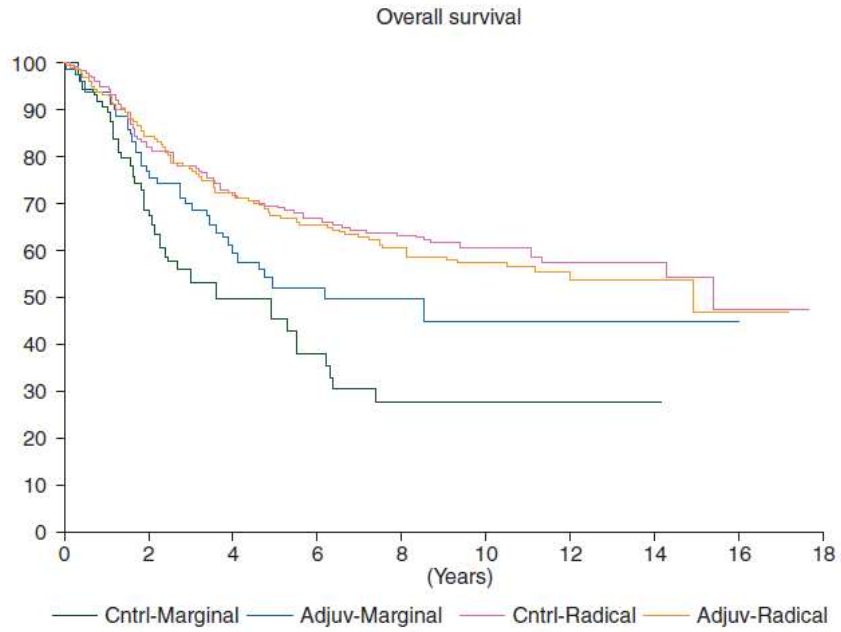


Figure 3: **Effects of adjuvant chemotherapy on overall survival for patients with different baseline prognostic factors**
O–E=observed minus expected.

Woll. Lancet Oncology 2012

Pooled Analysis of 2 EORTC trials (2014)

- 819 patients (AIM and CYVADIC)
- Benefit seen with chemotherapy only for marginal resections



Resection	Treatment	Patients (N)	Events (O)	Median (95% CI) (Years)	% at 10 Year(s) (95% CI)	Hazard ratio (95% CI)	*P*-value
Marginal	Control	74	45	4.87 (2.38, 6.20)	27.60 (15.84, 40.68)	1.00	0.0488
	Adjuvant	79	36	6.22 (3.93, N)	44.69 (30.01, 58.34)	0.64 (0.42, 1.00)	
Radical	Control	317	114	15.44 (9.38, N)	60.63 (54.36, 66.31)	1.00	0.5951
	Adjuvant	301	113	14.96 (8.13, N)	57.74 (51.13, 63.79)	1.07 (0.82, 1.39)	

Le Cesne. Annals of Oncology 2014

Neoadjuvant Histology Specific (2017)

- Epirubicin/Ifosfamide (no XRT) vs.
  - Myxoid liposarcoma: Trabectedin
  - Leiomyosarcoma: Gem/Dacarbazine
  - Synovial sarcoma: High dose Ifosfamide
  - MPNST: Ifosfamide/Etoposide
  - UPS: Gem/Tax

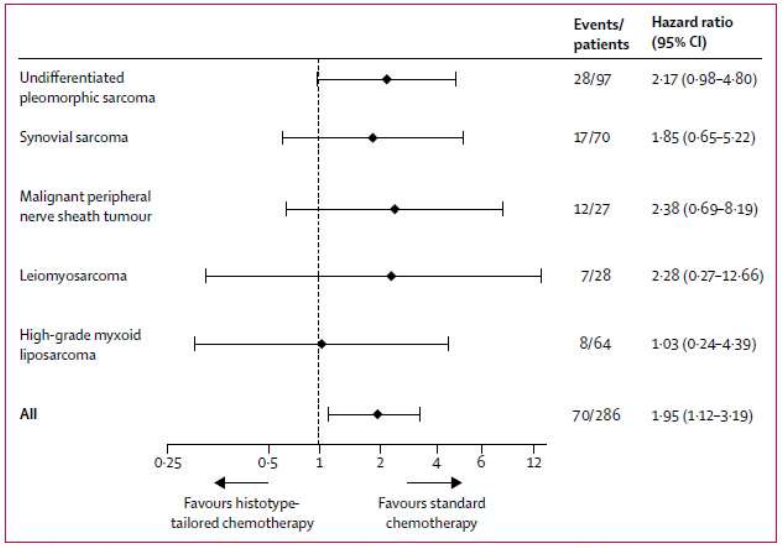


Figure 4: **Standard versus histotype-tailored chemotherapy in the five different histology subtypes**
Hazard ratios of disease-free survival were estimated with binary logistic models.

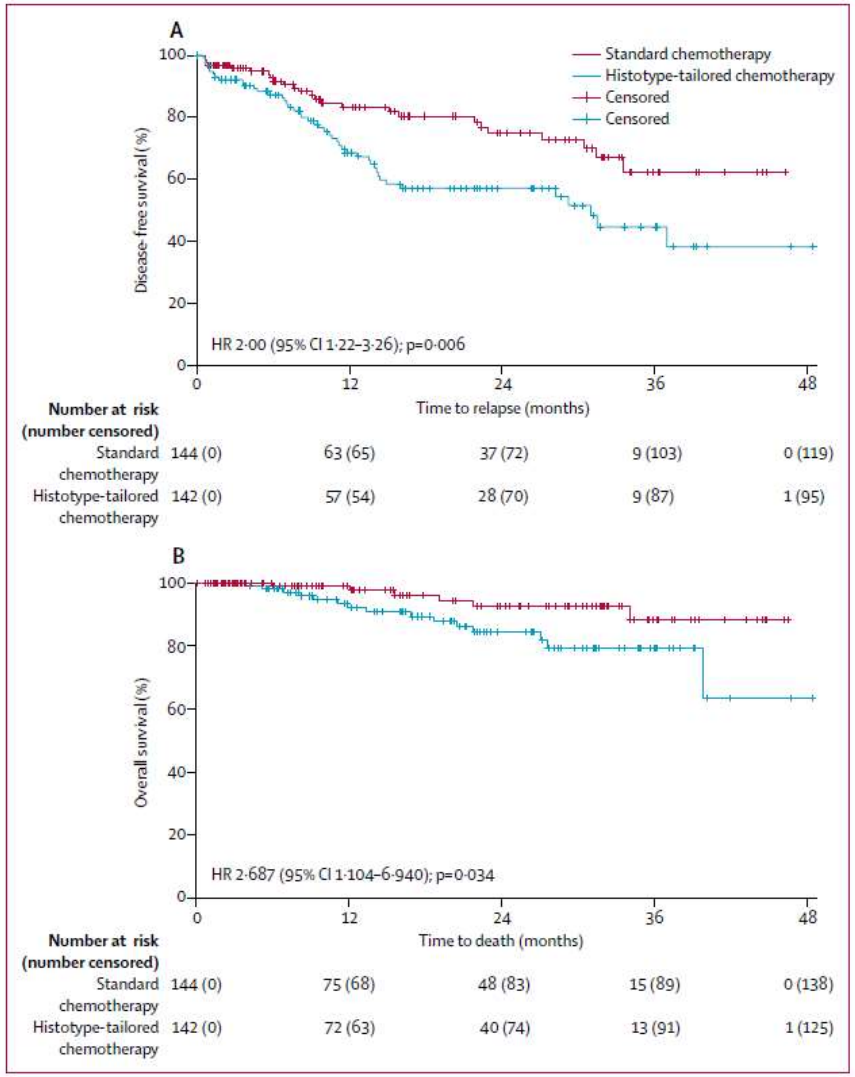


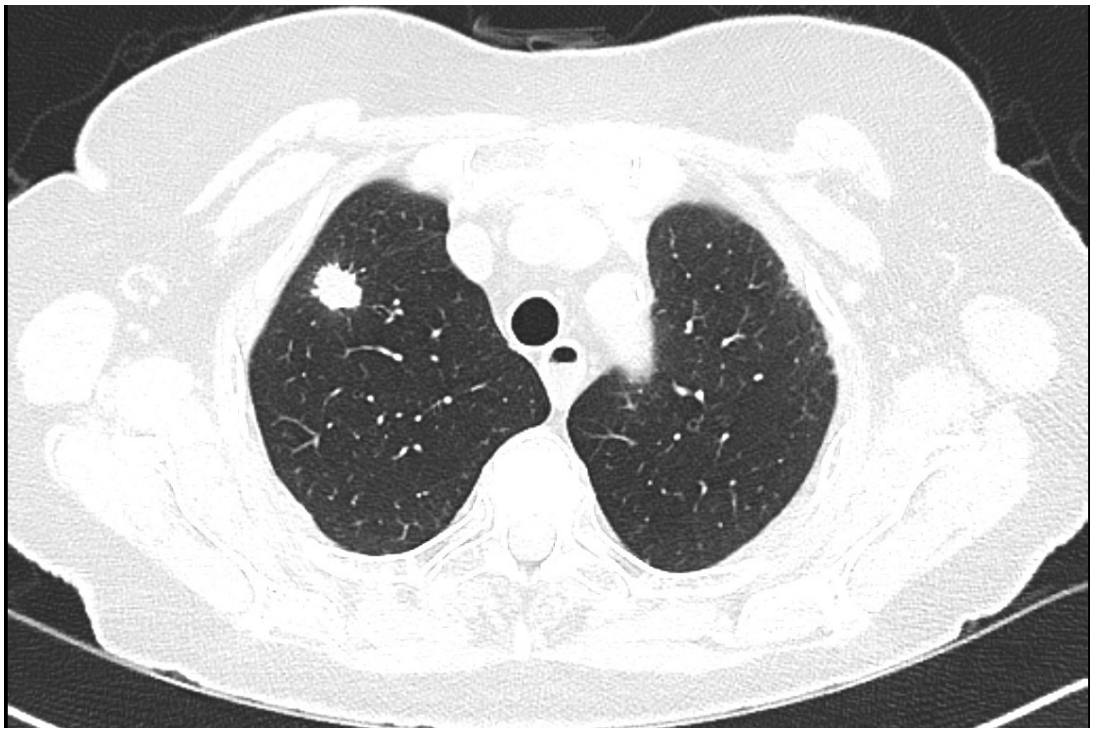
Figure 2: **Disease-free survival and overall survival at 46 months from randomisation**
(A) Disease-free survival. (B) Overall survival. HR=hazard ratio. Gronchi. Lancet Oncology 2017

Thoughts

- Neo/Adjuvant chemotherapy benefit is controversial and absolute survival benefit is from 0-10%
- If Neo/Adjuvant chemotherapy is given, need to give combined Doxorubicin + Ifosfamide
- Need to have discussion with patient about risk/benefit and that there is no clearly defined benefit to adjuvant chemotherapy

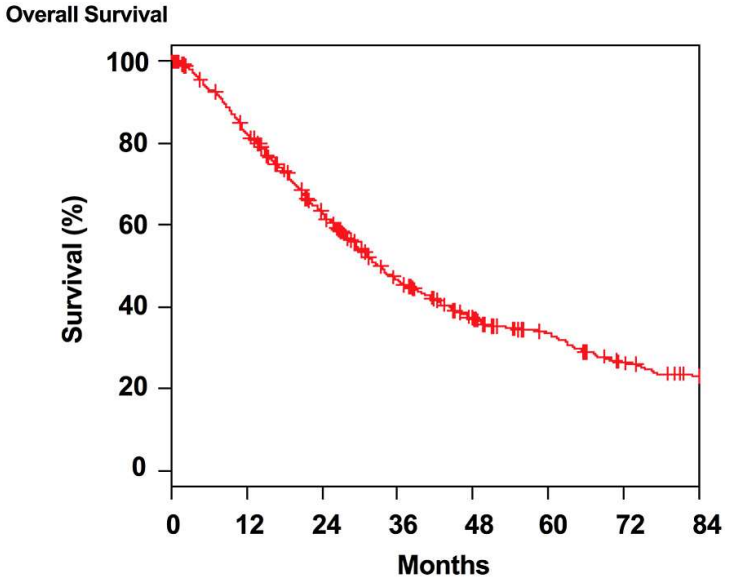
Metastatic Recurrence

- 1.5 years later on surveillance scans, 1.5cm RUL lung mass appears
- Next steps?

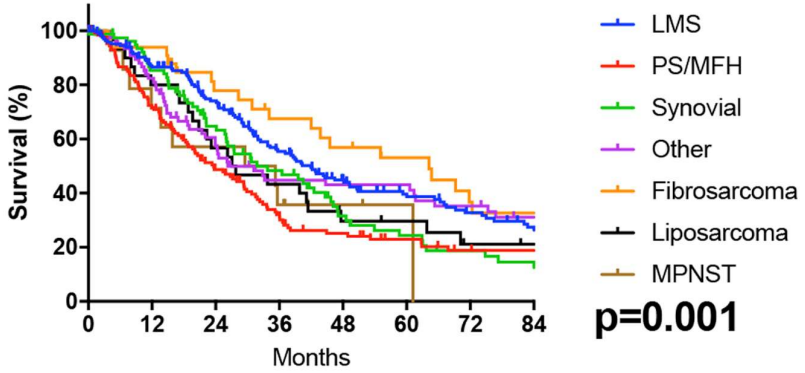


Metastectomy

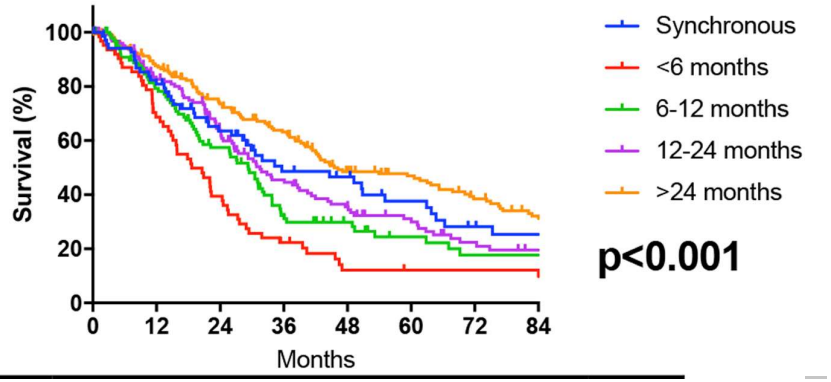
- Multiple studies have shown long term survival for oligometastatic resection of isolated pulmonary mets
- Chudgar JTCS 2017: 803 patients with metastatic sarcoma who underwent pulmonary metastectomy
  - mOS 33.2 months
  - 5 year OS/DFS 38%/35%



Primary Histology

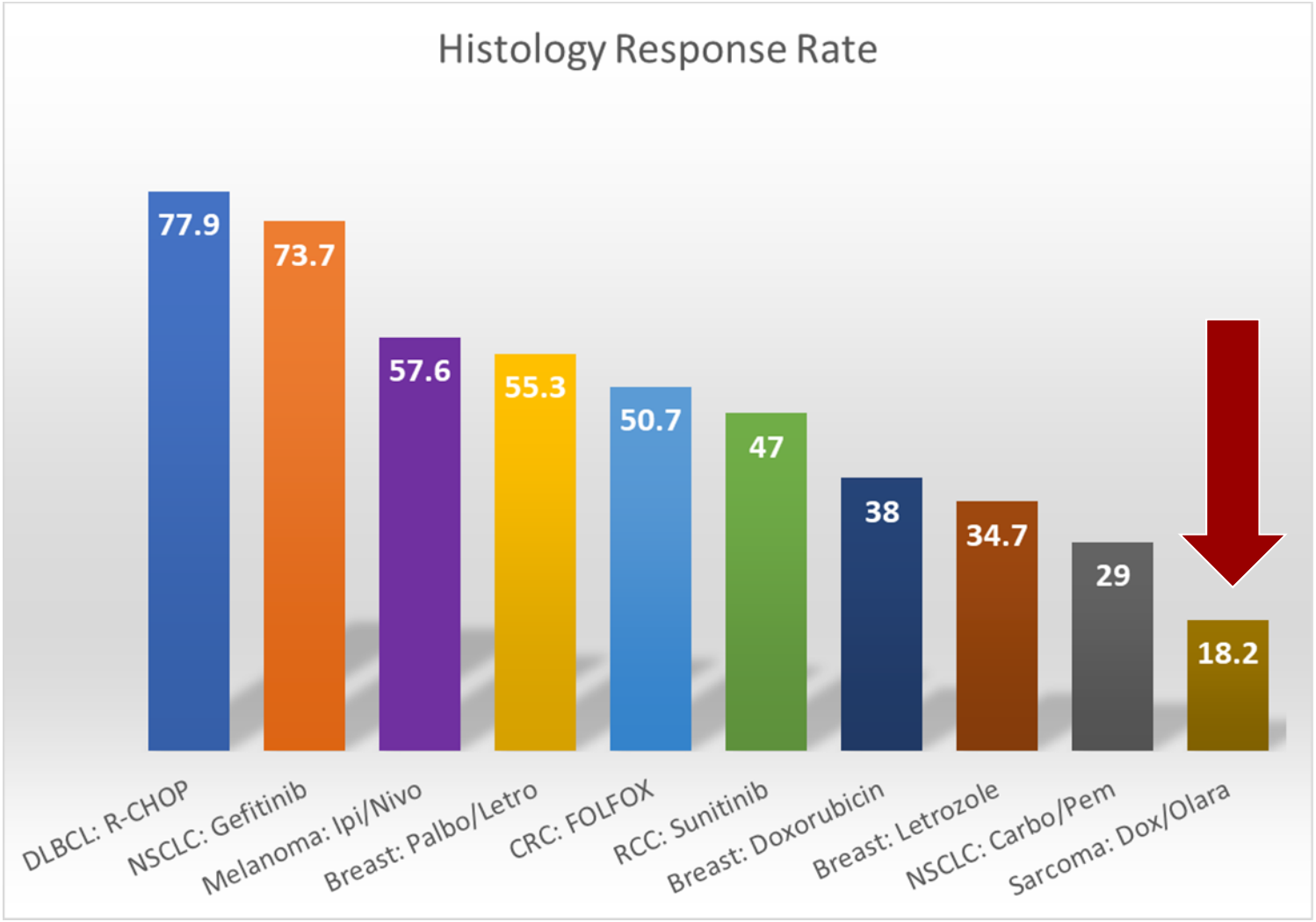


Disease-Free Interval



Concept: Metastatic Chemotherapy

Metastatic Chemotherapy

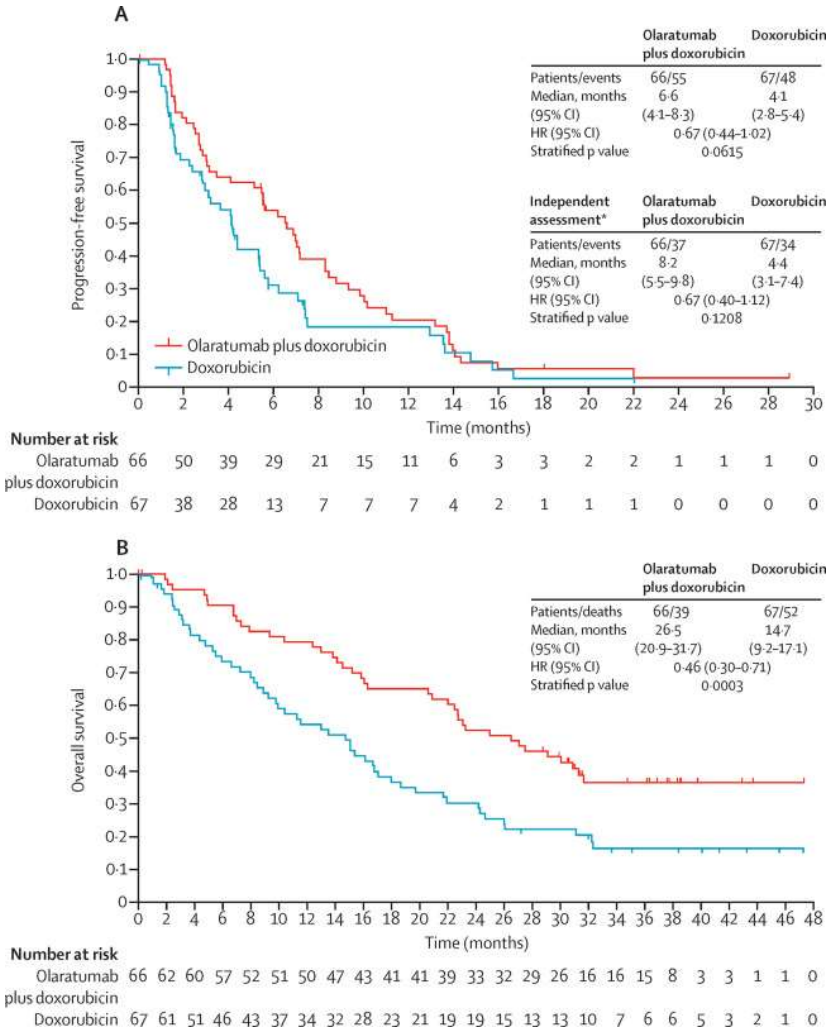


Metastatic Chemotherapy

- Accelerated Approval (2016): **Doxorubicin + Olaratumab**
- Addition of olaratumab (PDGFRα mAb) decreased risk of death by **54%** and improved median OS by **11.8 months**
- PFS improved by **2.5 months**

Table 1. Exploratory analysis of associations of biomarker and results for OS and PFS

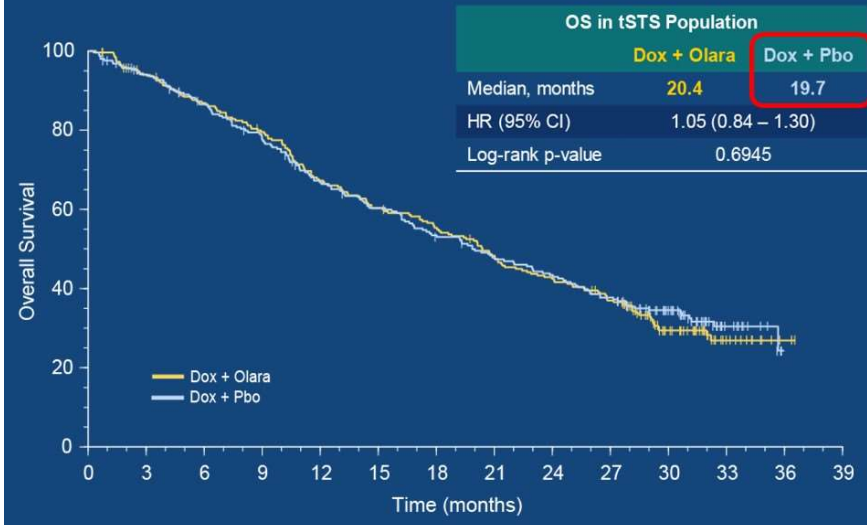
Marker	n	Median Relative Expression Value	PFS	OS	PFS	OS
			Hazard Ratio, 90% CI		*p*-Value(a), Interaction	
PDGFRa_Low	**38**	**1242.37**	**0.83 (0.45, 1.52)**	**0.38 (0.19, 0.76)**	**0.693**	**0.151**
PDGFRa_High	**38**		**1.01 (0.57, 1.81)**	**0.87 (0.46, 1.63)**		
CXCR4_Low	38	1167.24	0.48 (0.26-0.87)	0.32 (0.17-0.60)	0.021	0.041
CXCR4_High	39		1.61 (0.90-2.88)	1.01 (0.52-1.95)		
PDGFa_Low	37	449.20	0.53 (0.29-0.97)	0.35 (0.18-0.67)	0.121	0.059
PDGFa_High	38		1.23 (0.66-2.27)	1.04 (0.53-2.01)		
PDGFb_Low	38	401.98	0.51 (0.28-0.91)	0.35 (0.19-0.66)	0.036	0.147
PDGFb_High	38		1.49 (0.83-2.69)	0.79 (0.41-1.56)		
VEGFa_Low	38	2283.82	0.52 (0.29-0.92)	0.49 (0.25-0.94)	0.054	0.66
VEGFa_High	38		1.39 (0.77-2.52)	0.63 (0.32-1.24)		

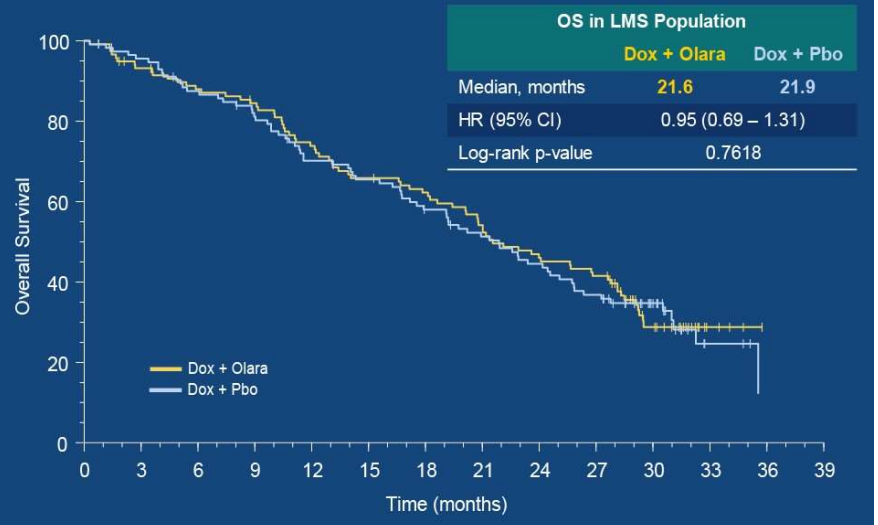


Tap. Lancet Oncology 2016

ANNOUNCE Phase III Confirmatory Trial

Overall Survival: tSTS and LMS Populations





Dox, doxorubicin; LMS, leiomyosarcoma; Olara, olaratumab; OS, overall survival; Pbo, placebo; tSTS, total Soft Tissue Sarcoma

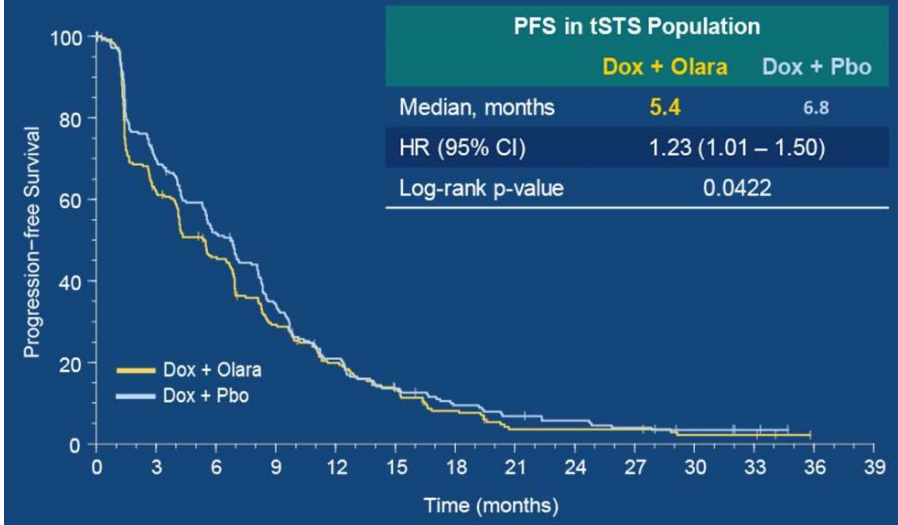
PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: William D Tap, MD

18

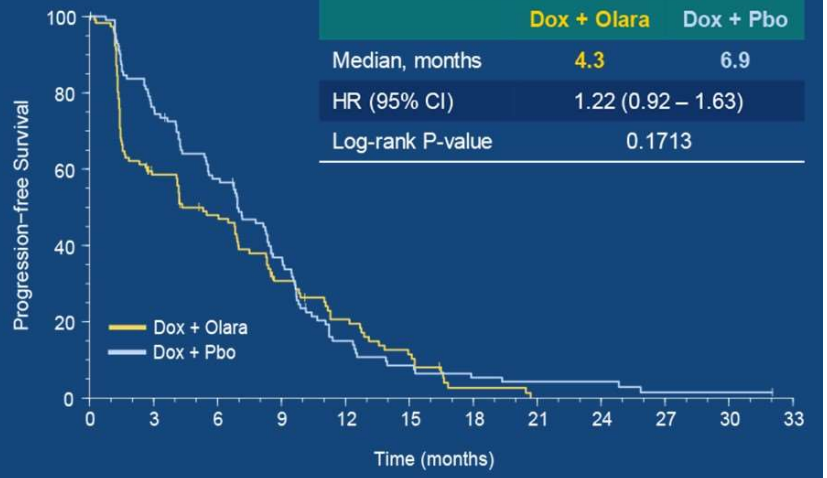
ANNOUNCE Phase III Confirmatory Trial

Progression-free Survival: tSTS and LMS Populations



PFS in tSTS Population

	Dox + Olara	Dox + Pbo
Median, months	5.4	6.8
HR (95% CI)	1.23 (1.01 – 1.50)	
Log-rank p-value	0.0422	



PFS in LMS Population

	Dox + Olara	Dox + Pbo
Median, months	4.3	6.9
HR (95% CI)	1.22 (0.92 – 1.63)	
Log-rank P-value	0.1713	

Dox, doxorubicin; Olara, olaratumab; Pbo, placebo; PFS, progression-free survival; tSTS, total Soft Tissue Sarcoma

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: William D Tap, MD

20

ANNOUNCE Phase III Confirmatory Trial

Overall Response Rate: tSTS and LMS Populations

Response rate, %	tSTS		LMS	
	Doxorubicin + Olaratumab (N=258)	Doxorubicin + Placebo (N=251)	Doxorubicin + Olaratumab (N=119)	Doxorubicin + Placebo (N=115)
Best overall response				
Complete response (CR)	0.8	0.4	0.8	0
Partial response (PR)	13.2	17.9	12.6	22.6
Stable disease (SD)	53.5	57.4	49.6	60.0
Progressive disease	27.1	20.7	33.6	14.8
Objective response rate	14.0	18.3	13.4	22.6
	p=0.1837		p=0.0890	
Disease control rate (CR+PR+SD)	67.4	75.7	63.0	82.6
	p=0.0595		p=0.0011	

LMS, leiomyosarcoma; tSTS, total soft tissue sarcoma

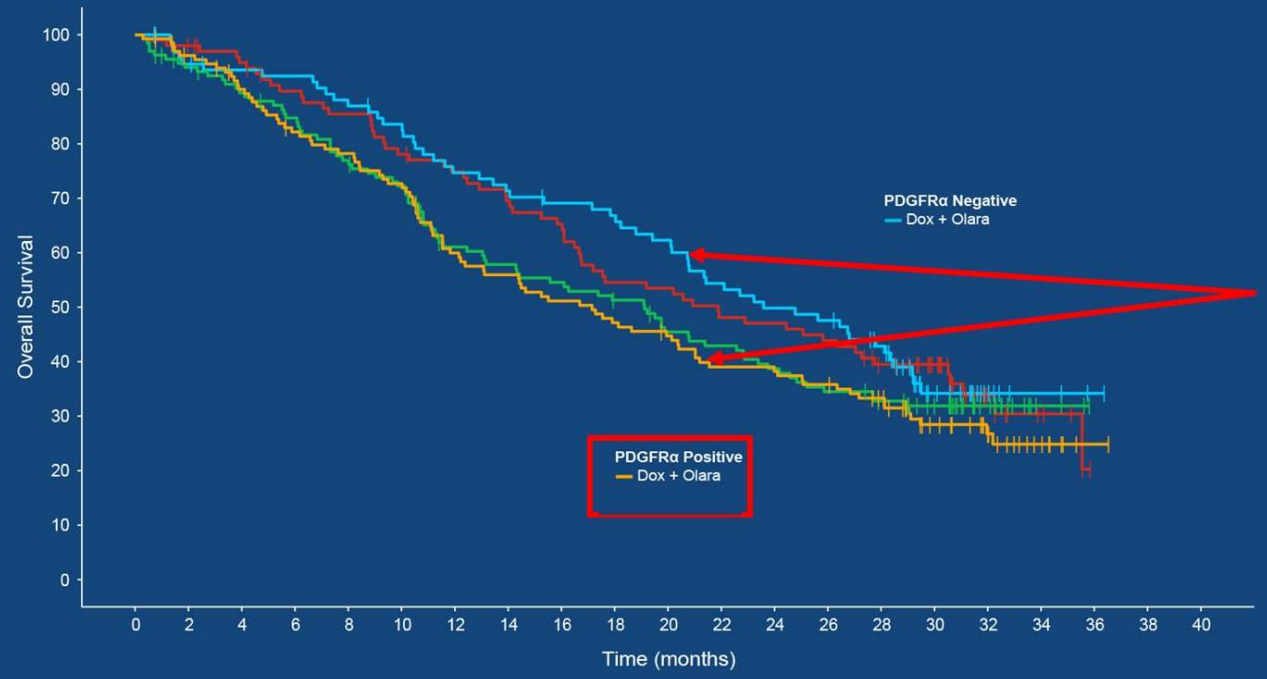
PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: William D Tap, MD

21

ANNOUNCE Phase III Confirmatory Trial

Exploratory Analyses: OS by Treatment and PDGFRα IHC Status - tSTS

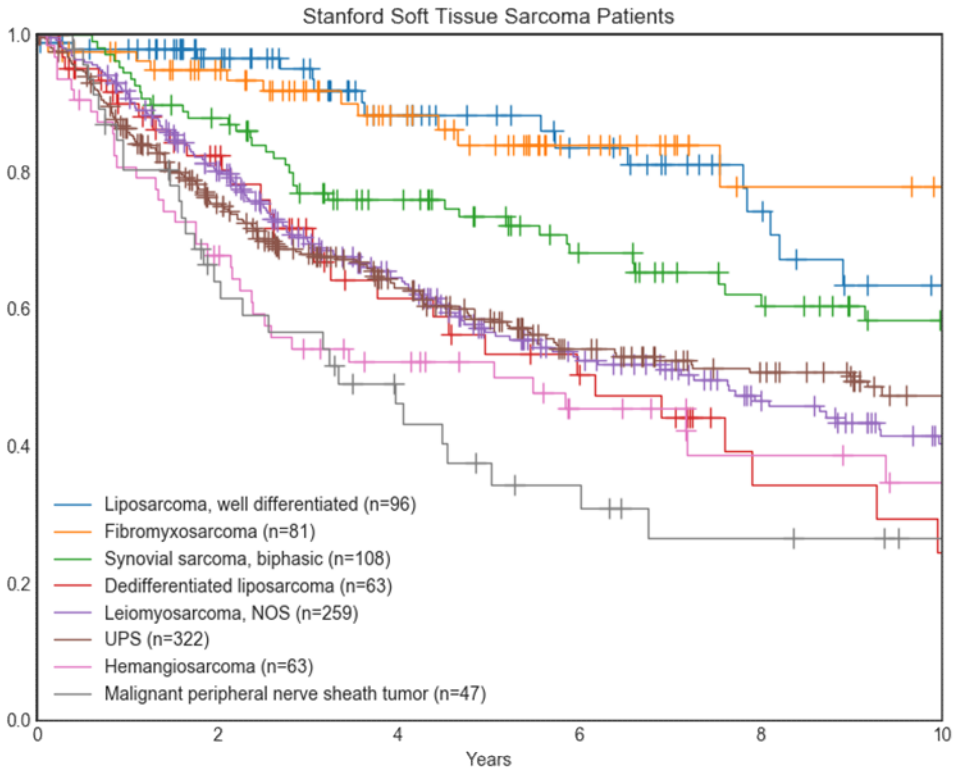


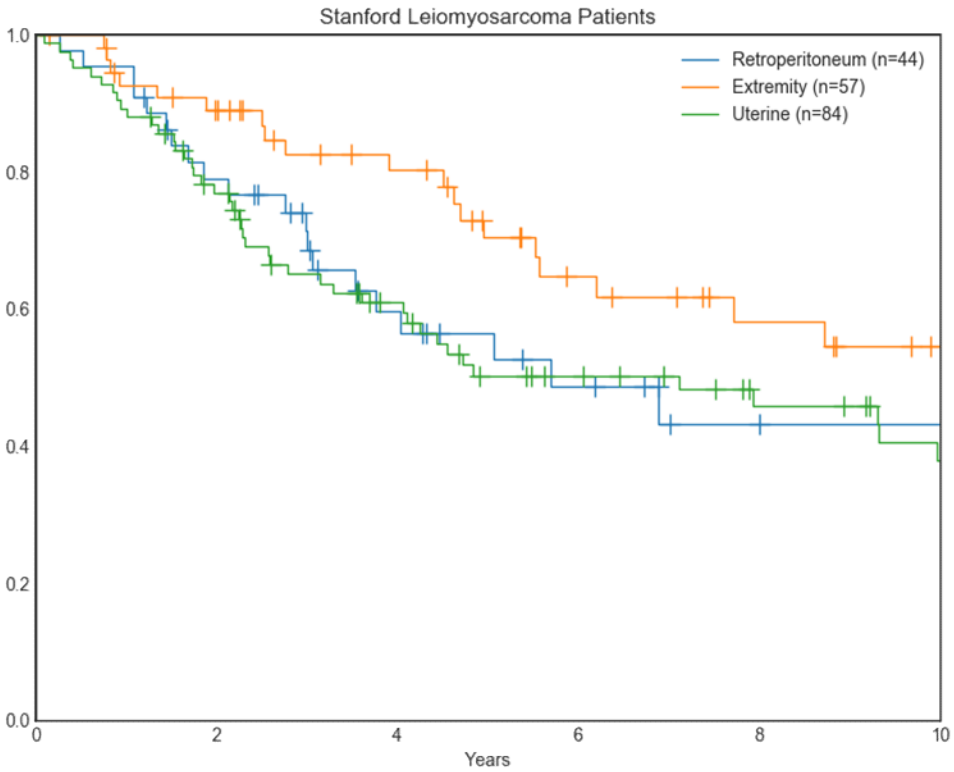
Dox, doxorubicin; IHC, immunohistochemistry; Olara, olaratumab; OS, overall survival; Pbo, placebo; PDGFR, platelet-derived growth factor receptor; tSTS, total soft tissue sarcoma

23

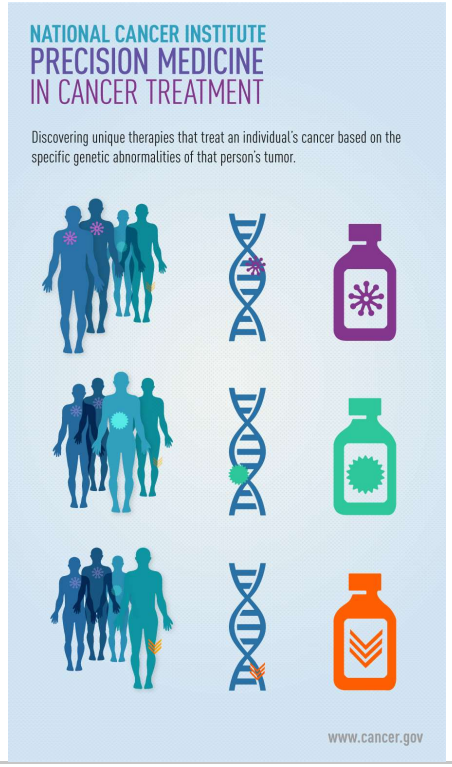
Weakness of Sarcoma Trials

- Sarcomas have widely different natural histories!





Concept: Precision Oncology

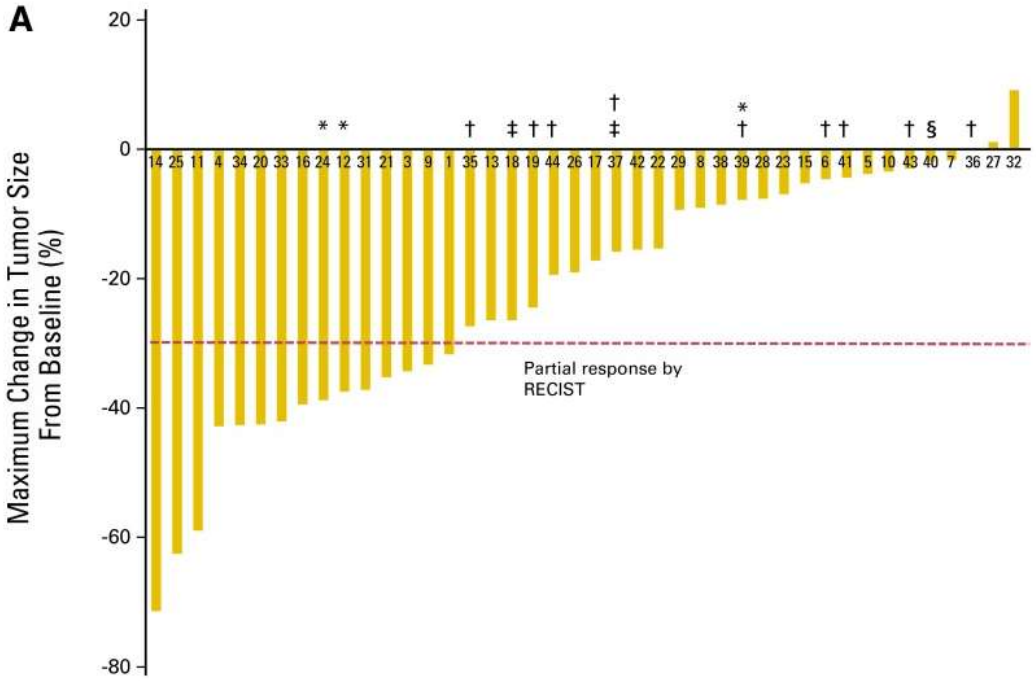


Sarcoma Translocations

Translocation	Genes
Ewing's sarcoma (OMIM#133450)	
t(11;22)(q24;q12)	*EWSR1-FLI1*
t(21;22)(q22;q12)	*EWSR1-ERG*
t(7;22)(p22;q12)	*EWSR1-ETV1*
t(17;22)(q12;q12)	*EWSR1-ETV4*
t(2;22)(q35;q12)	*EWSR1-FEV*
t(2;16)(q35;p11)	*FUS-FEV*
t(16;21)(p11;q24)	*FUS-ERG*
Ewing-like undifferentiated sarcoma (OMIM#300485)	
t(X;X)(p11;p11)	*BCOR-CCNB3*
Clear cell sarcoma (OMIM#123803)	
t(12;22)(q13;q12)	*EWSR1-ATF1*
Desmoplastic small round cell tumor of the abdomen (OMIM#133450)	
t(11;22)(p13;q12)	*EWSR1-WT1*
Myxoid chondrosarcoma (OMIM#600542)	
t(9;22)(q22-31;q11-12)	*EWSR1-NR4A3*
Myxoid liposarcoma (OMIM#126337, #137070)	
t(12;16)(q13;p11)	*FUS-CHOP* (*FUS-DDIT3*)
t(12;22)(q13;q12)	*EWSR1-CHOP* (*EWSR1-DDIT3*)
Alveolar rhabdomyosarcoma (OMIM#268220)	
t(2;13)(q35;q14)	*PAX3-FOXO1A**
t(1;13)(p36;q14)	*PAX7-FOXO1A**
Synovial sarcoma (OMIM#312820)	
t(X;18)(p11;q11)	*SS18-SSX1*, *SSX2*, or *SSX4*
Dermatofibrosarcoma protuberans (OMIM#607907)	
t(17;22)(q22;q13)	*COL1A1-PDGFB*
Congenital fibrosarcoma (OMIM#191316)	
t(12;15)(p13;q25)	*ETV6-NTRK3*
Inflammatory myofibroblastic tumor	
2p23 rearrangements	*TMP3-ALK*
	TMP4-ALK
Alveolar soft part sarcoma (OMIM#606243)	
t(X;17)(p11.2;q25)	*ASPL-TFE3*
Solitary fibrous tumor (OMIM#602381)	
Inversion 12q13	*NAB2-STAT6*
Epithelioid hemangioendothelioma	
t(1;3)(p36;q25)	*WWTR1-CAMTA1*

Sarcoma Targeted Therapy

- **Alveolar Soft Part Sarcoma**: ASPL-TFE3
- Highly sensitive to VEGF inhibition (cedarinib)

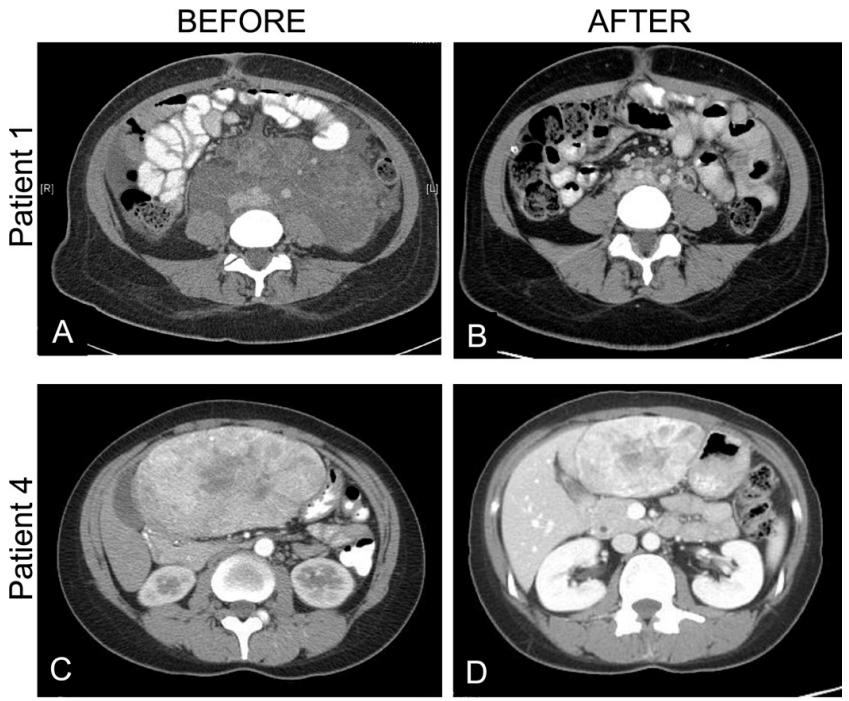


Kummar. JCO 2013

Sarcoma Targeted Therapy

- **Perivascular epitheliod cell tumors** (PEComas)
- Frequent loss of TSC1/2 (~80%), leads to marked enhancement of mTORC1 signaling

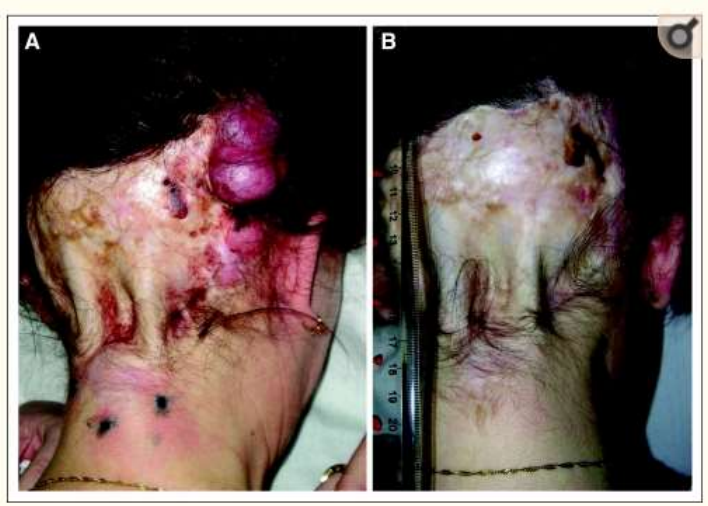
Treatment with **sirolimus** or **everolimus**

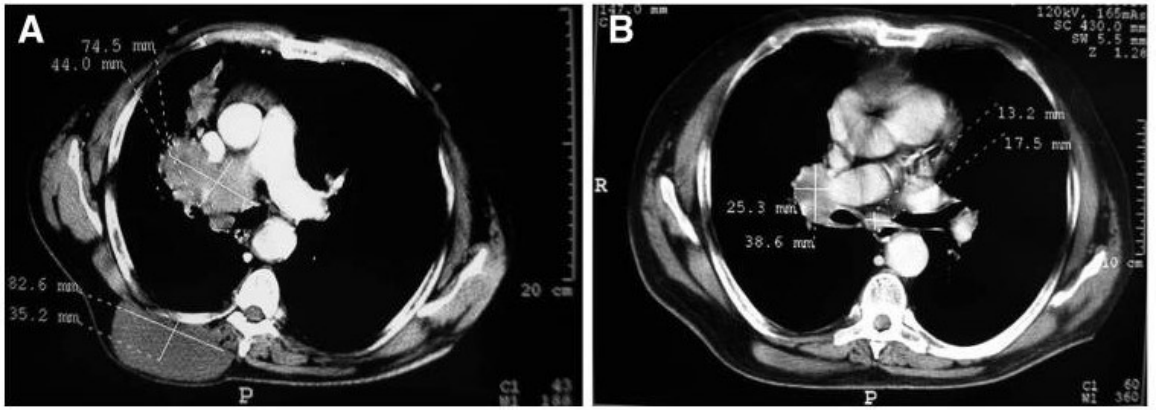


Dickson. Int J Cancer 2013

Sarcoma Targeted Therapy

- **Dermatofibrosarcoma Protuberans (DFSP)**
- Dermal sarcoma that grows indolently and rarely metastasizes
- Characteristics COL1A1-PDGFB fusion
- **Imatinib** has a response rate of **46%**

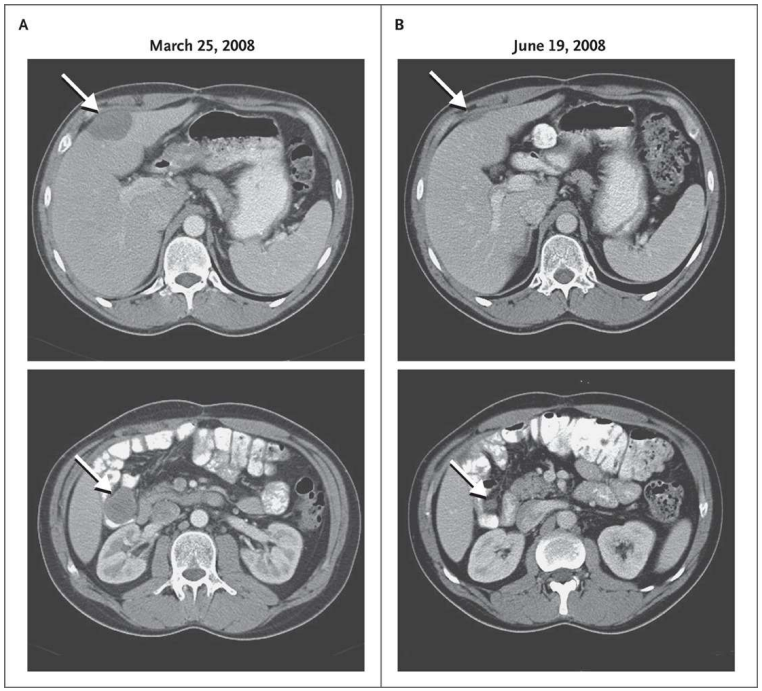




Rutkowski. JCO. 2010

Sarcoma Targeted Therapy

- **Inflammatory myobfibroblastic tumor** (IMT)
- TPM3/4-ALK translocation (50%)
- Sensitivity to crizotinib

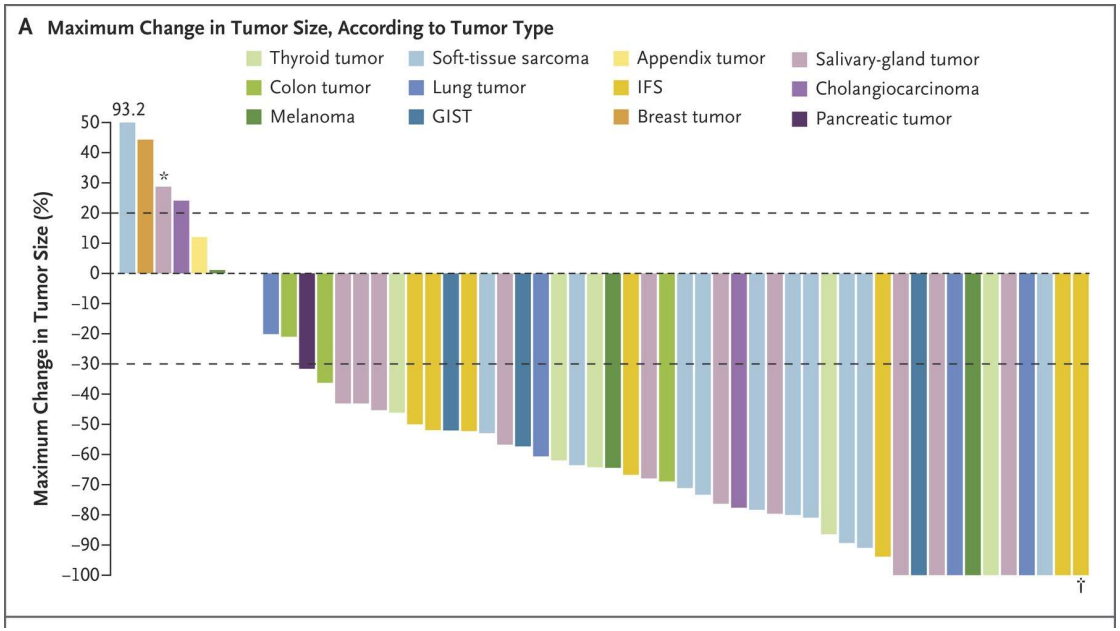


Butrynski. NEJM 2010

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children



ORR 80%
mDOR not reached (8.3 months median f/u)

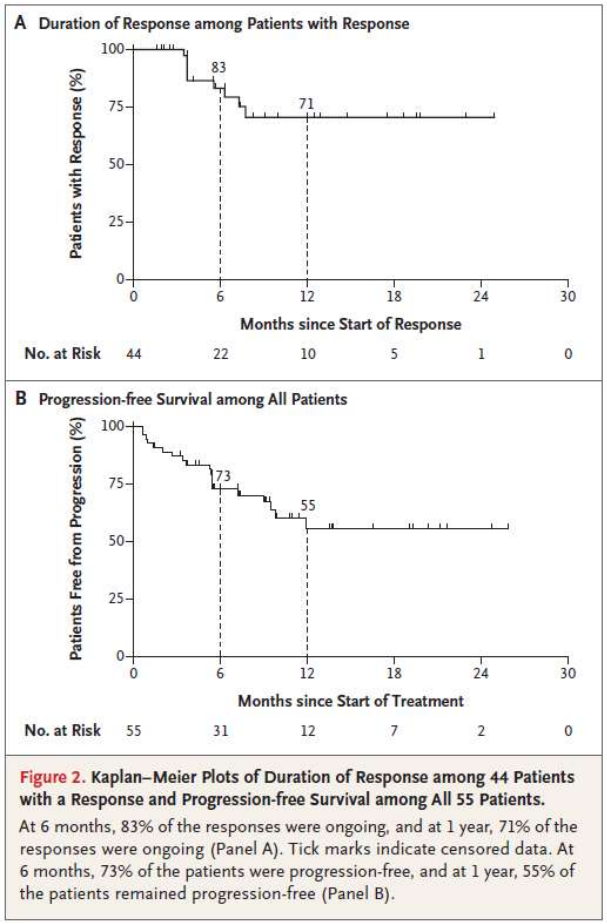
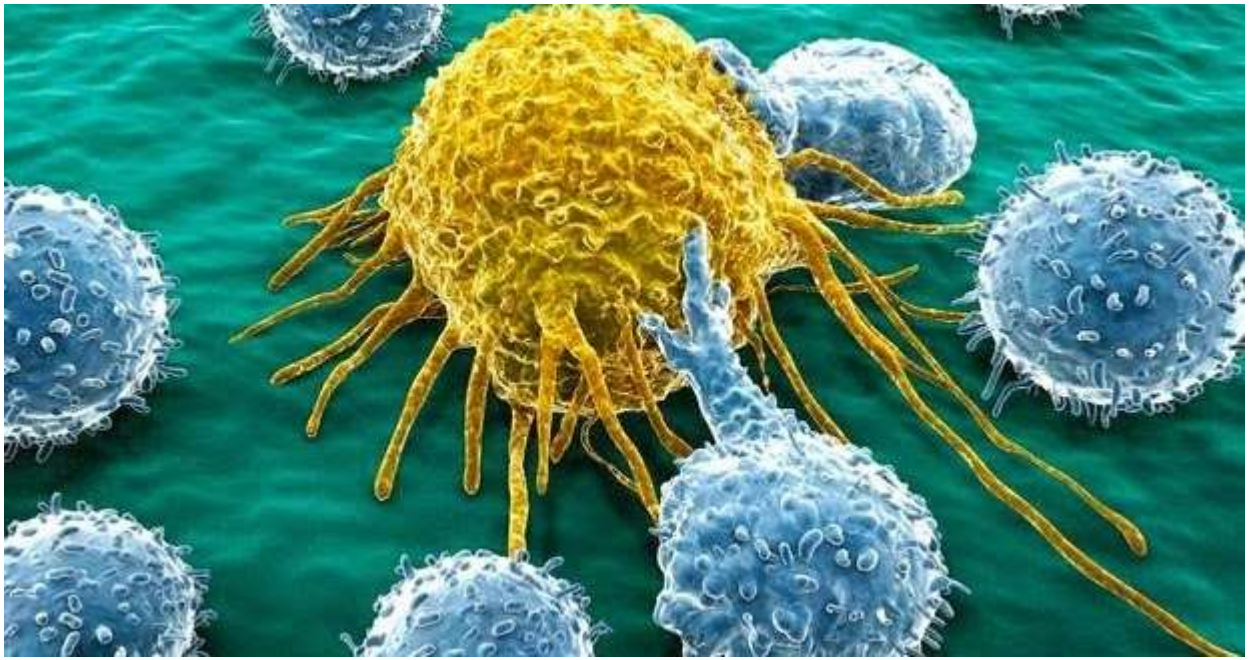


Figure 2. Kaplan–Meier Plots of Duration of Response among 44 Patients with a Response and Progression-free Survival among All 55 Patients.

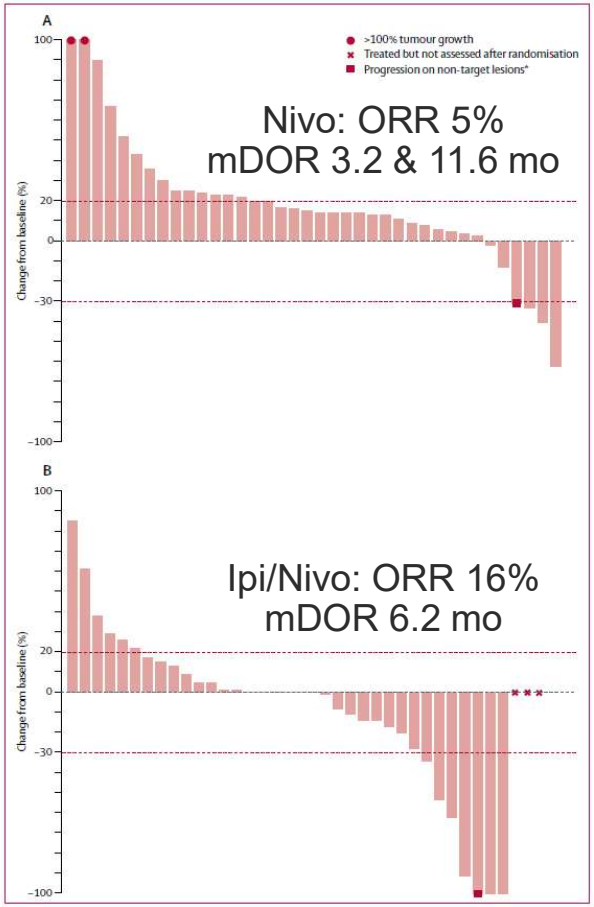
At 6 months, 83% of the responses were ongoing, and at 1 year, 71% of the responses were ongoing (Panel A). Tick marks indicate censored data. At 6 months, 73% of the patients were progression-free, and at 1 year, 55% of the patients remained progression-free (Panel B).

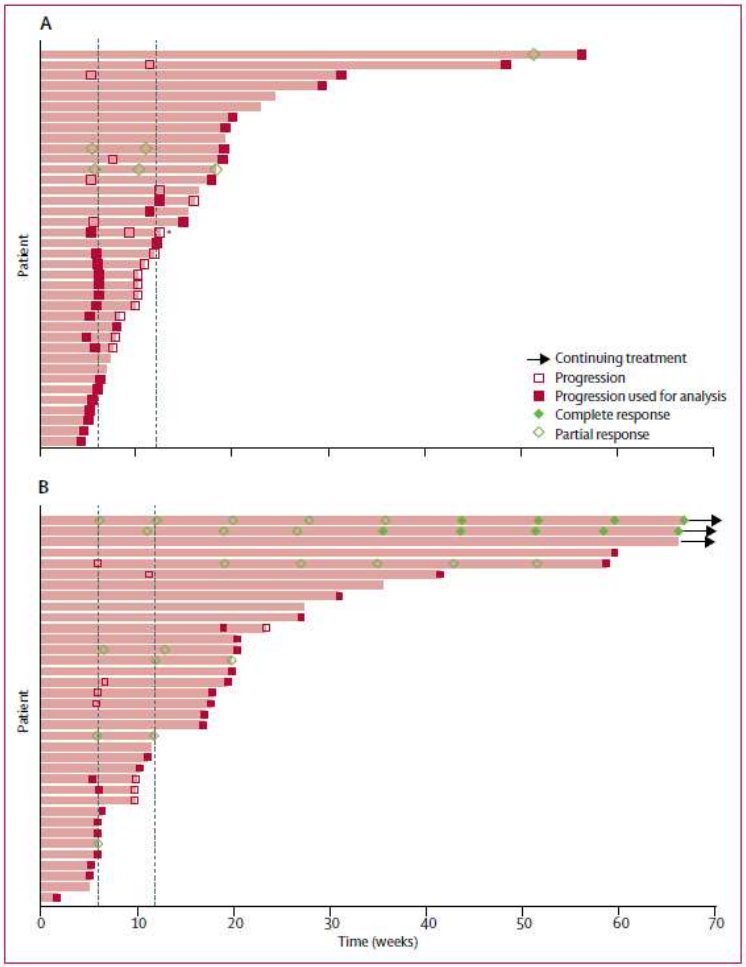
Concept: Immunotherapy



Immunotherapy in Sarcoma

- ALLIANCE trial of 96 sarcoma patients randomized to **Ipi/Nivo** vs **Nivo** (D'Angelo. Lancet Oncology 2018)





Arm	Patient	Histology	Time to 1st Response[a]	Duration of Response[ab]	End of Treatment Reason	Confirmed Response
1[c]	1	**Alevolar**	5.6	12.6	Adverse Events	Yes, PR
	2	**Leimoyosarcoma (LMS), non-uterine**	5.3	13.7	PD	Yes, PR
	3	**Other/recurrent sarcoma**	51.1	5.0	PD	No
2[c]	1	**Undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma (UPS/MFH)**	6.0	0.1	Adverse Events	No
	2	**Myxofibrosarcoma**	6.1	61.3	Ongoing	Yes, PR converted to CR within 8.5 months of PR
	3	**UPS/MFH**	6.6	14.0	PD	Yes, PR
	4	**LMS, uterine**	11.1	55.7	Ongoing	Yes, PR converted to CR within 2.5 months
	5	**Angiosarcoma**	5.9	6.0	Adverse Events	Yes, PR
	6	**LMS, non-uterine**	19.3	40.0	PD	Yes, PR
	7	**UPS/MFH**	12.0	8.0	Treated for other complicating disease (Radiation)	Yes, PR

a) In weeks.
b) Duration of Response censored at last disease assessment during treatment
c) Arm 1 is monotherapy; Arm 2 is combination therapy.

Summary

- Soft tissue sarcomas are rare but very diverse
- Adjuvant chemotherapy is controversial
- New treatment options needed for metastatic sarcoma
- Targeted therapy can be effective in a defined subset of patients
- Immunotherapy effective in a minority patients, need to further define a biomarker to predict response