Soft Tissue Sarcoma

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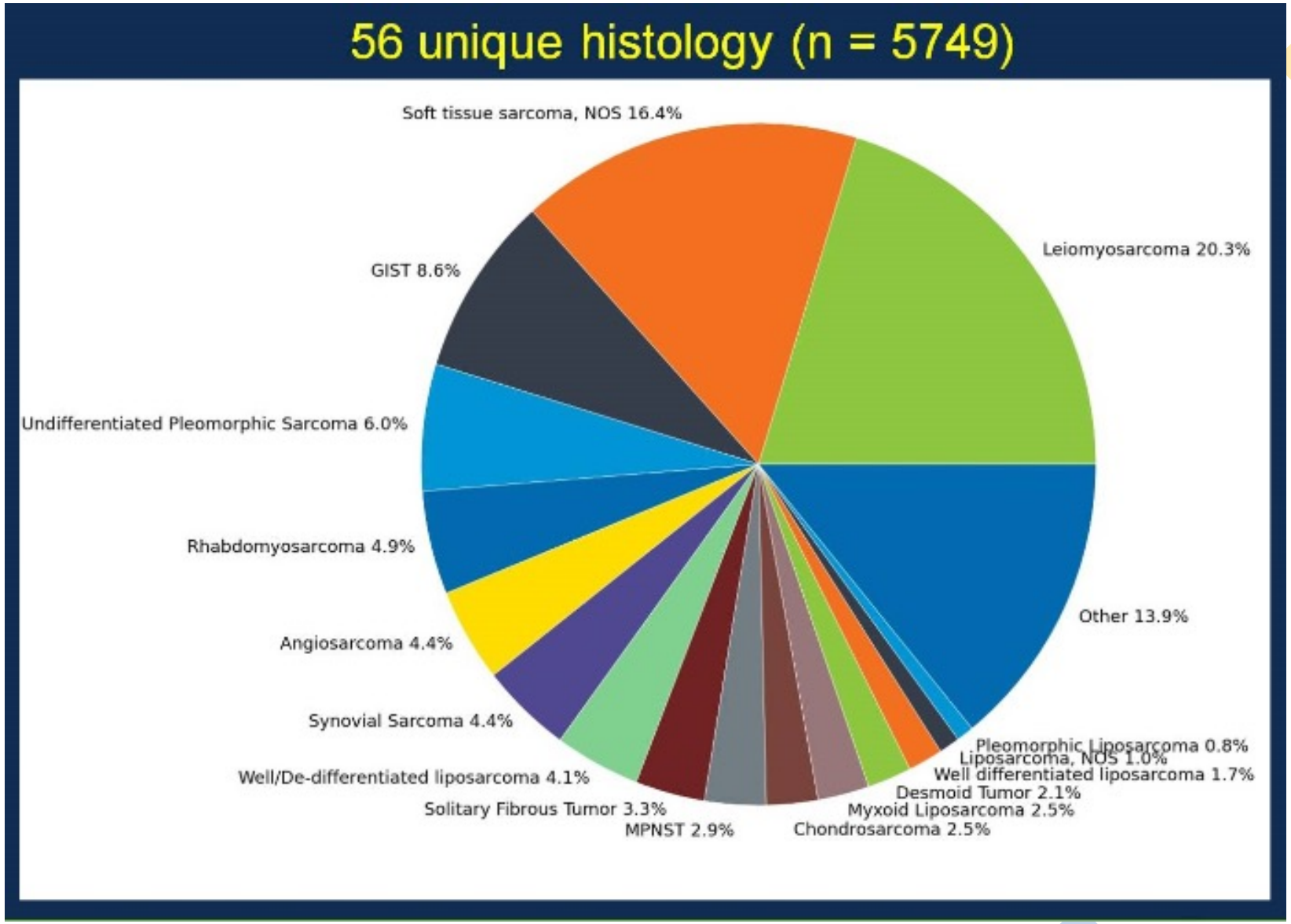
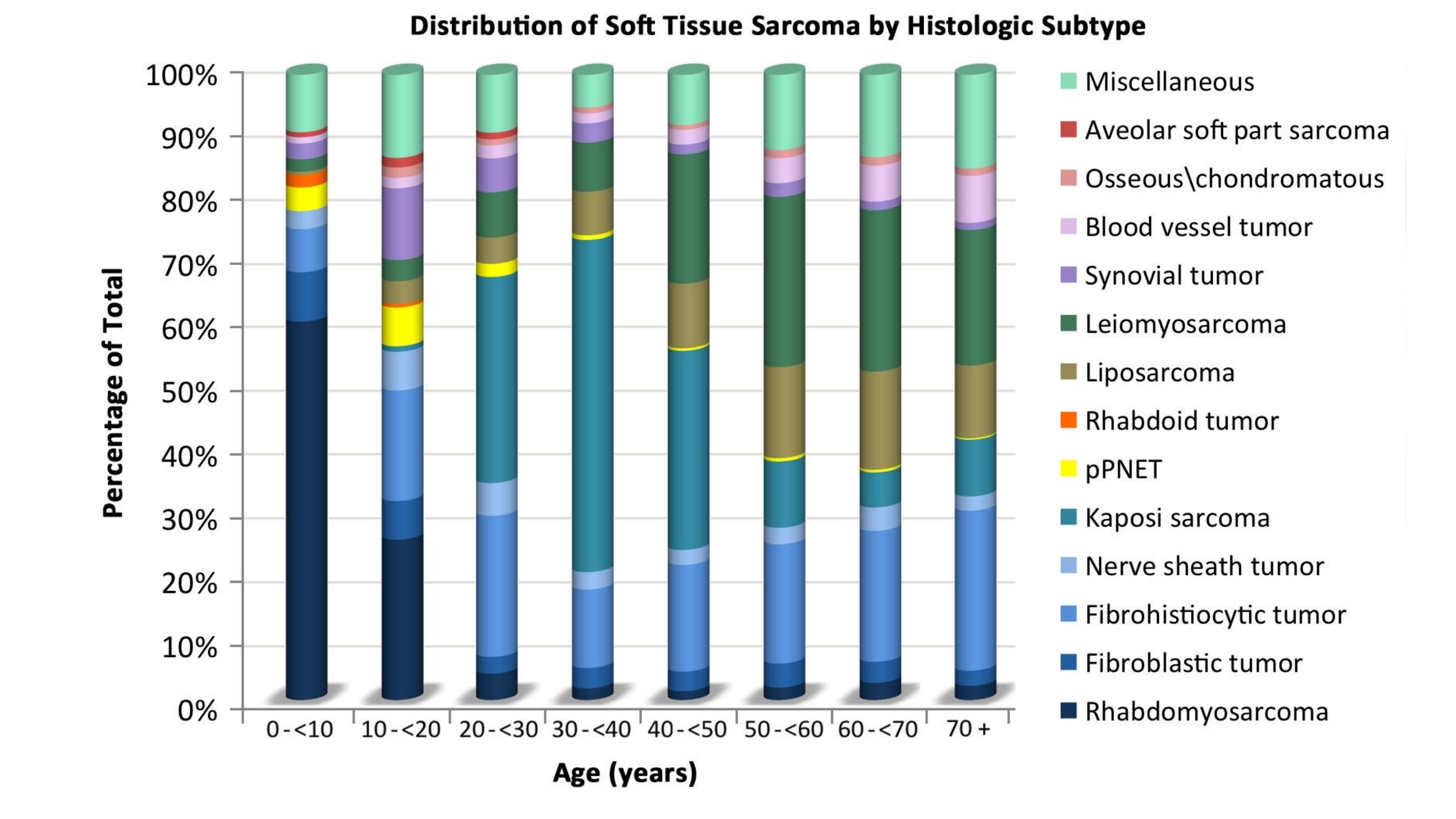
Soft Tissue Sarcoma 2022 ACS estimates

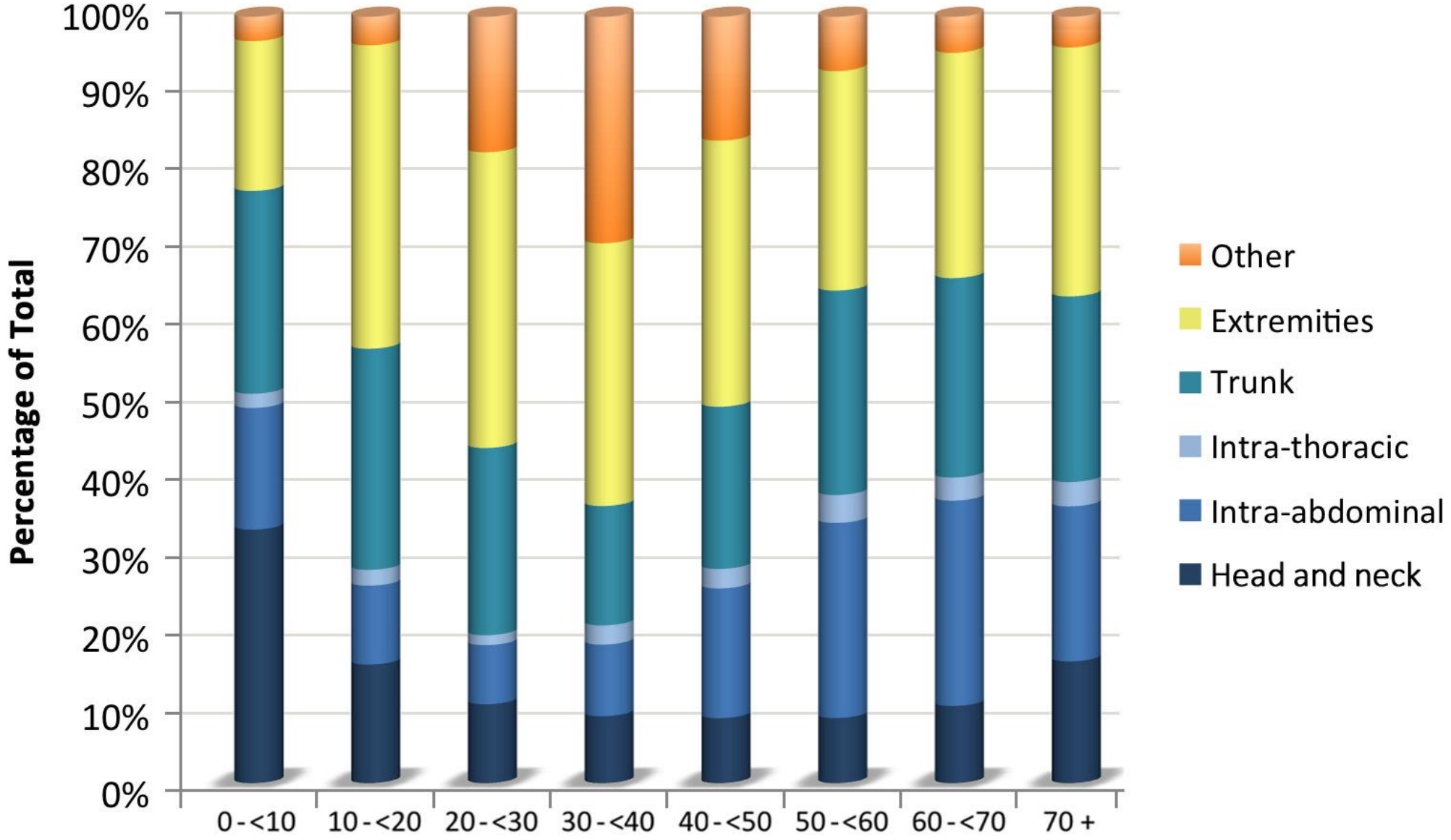
Incidence	13,190
Annual Deaths	5,130
5 yr survival	65%

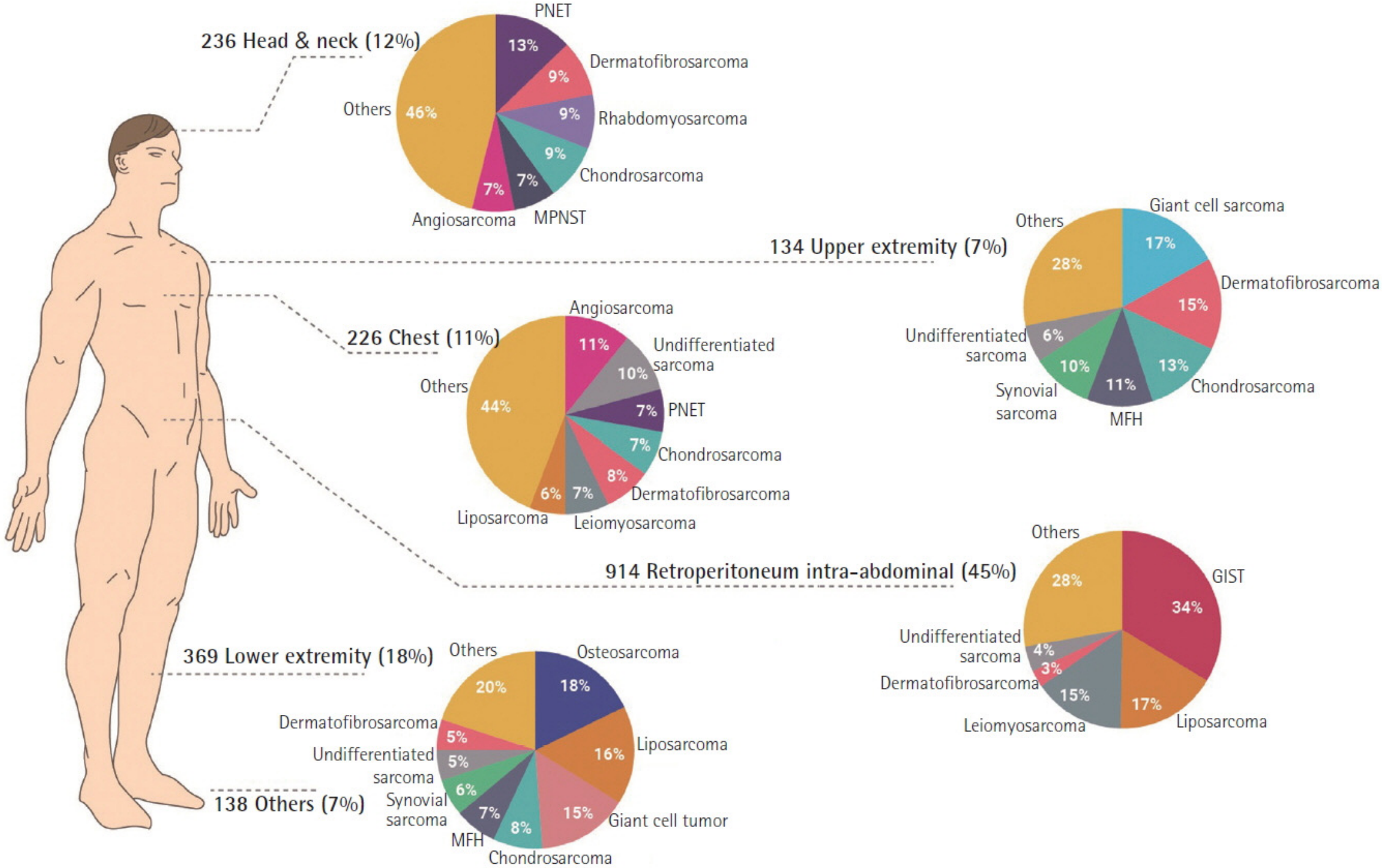
Pitfalls in Sarcoma Treatment and Research

- Extensive variation in histologic subtypes
  - Descriptor “soft tissue sarcoma” is not a single entity
  - Specific molecular alterations may identify unique tumor types
  - Discordant diagnoses among pathologists at different centers problematic (≈30%)
  - Similar molecular alterations may occur with different morphologic appearance (e.g., NTRK fusion)
- Incidence across the age spectrum from childhood to late adulthood
  - Distinct histologies occur in various age ranges
- Tumors of similar histology may occur in disparate locations complicating surgical access and local control


56 unique histology (n = 5749)
Soft tissue sarcoma, NOS 16.4%
Leiomyosarcoma 20.3%
GIST 8.6%
Undifferentiated Pleomorphic Sarcoma 6.0%
Rhabdomyosarcoma 4.9%
Angiosarcoma 4.4%
Synovial Sarcoma 4.4%
Well/De-differentiated liposarcoma 4.1%
Solitary Fibrous Tumor 3.3%
MPNST 2.9%
Chondrosarcoma 2.5%
Myxoid Liposarcoma 2.5%
Desmoid Tumor 2.1%
Well differentiated liposarcoma 1.7%
Liposarcoma, NOS 1.0%
Pleomorphic Liposarcoma 0.8%
Other 13.9%


Distribution of Soft Tissue Sarcoma by Histologic Subtype
Percentage of Total
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0 - <10
10 - <20
20 - <30
30 - <40
40 - <50
50 - <60
60 - <70
70 +
Age (years)
Miscellaneous
Aveolar soft part sarcoma
Osseous\chondromatous
Blood vessel tumor
Synovial tumor
Leiomyosarcoma
Liposarcoma
Rhabdoid tumor
pPNET
Kaposi sarcoma
Nerve sheath tumor
Fibrohistiocytic tumor
Fibroblastic tumor
Rhabdomyosarcoma


Percentage of Total
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0 - <10
10 - <20
20 - <30
30 - <40
40 - <50
50 - <60
60 - <70
70 +
Other
Extremities
Trunk
Intra-thoracic
Intra-abdominal
Head and neck


236 Head & neck (12%)
PNET
13%
Dermatofibrosarcoma
9%
Rhabdomyosarcoma
9%
Chondrosarcoma
9%
MPNST
7%
Angiosarcoma
7%
Others
46%
134 Upper extremity (7%)
Giant cell sarcoma
17%
Dermatofibrosarcoma
15%
Chondrosarcoma
13%
MFH
11%
Synovial sarcoma
10%
Undifferentiated sarcoma
6%
Others
28%
226 Chest (11%)
Angiosarcoma
11%
Undifferentiated sarcoma
10%
PNET
7%
Chondrosarcoma
7%
Dermatofibrosarcoma
8%
Leiomyosarcoma
7%
Liposarcoma
6%
Others
44%
914 Retroperitoneum intra-abdominal (45%)
GIST
34%
Liposarcoma
17%
Leiomyosarcoma
15%
Dermatofibrosarcoma
3%
Undifferentiated sarcoma
4%
Others
28%
369 Lower extremity (18%)
Osteosarcoma
18%
Liposarcoma
16%
Giant cell tumor
15%
Chondrosarcoma
8%
MFH
7%
Synovial sarcoma
6%
Undifferentiated sarcoma
5%
Dermatofibrosarcoma
5%
Others
20%
138 Others (7%)

Primary Therapy for STS

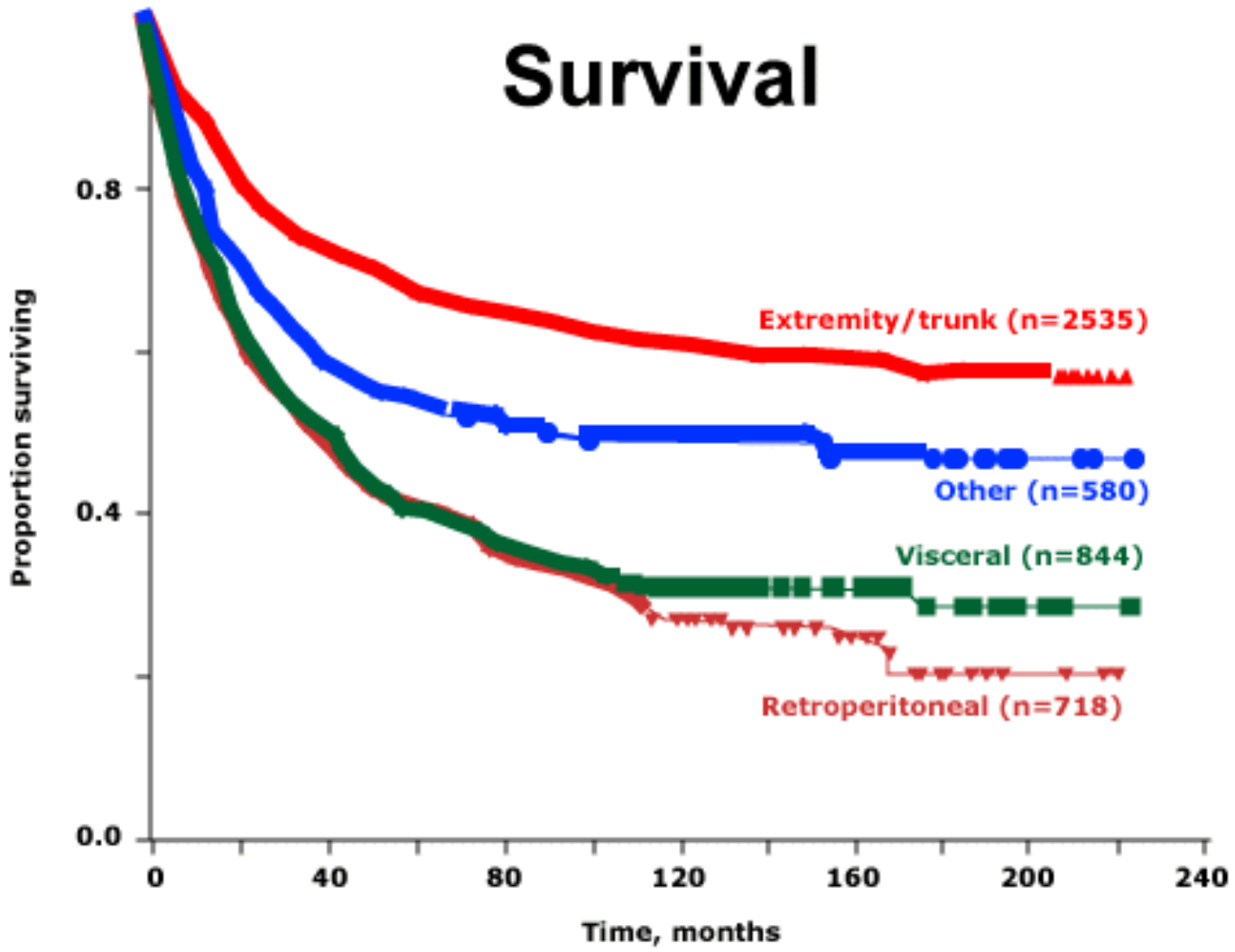
Requires the expertise of multiple disciplines

- Orthopedic Oncology/Surgical Oncology
- Radiation Oncology
- Adult Medical or Pediatric Oncology

Extensive reliance on expert pathology

Availability of molecular/genomic testing

MSKCC
1982-2001



Survival in primary soft tissue sarcoma according to primary site

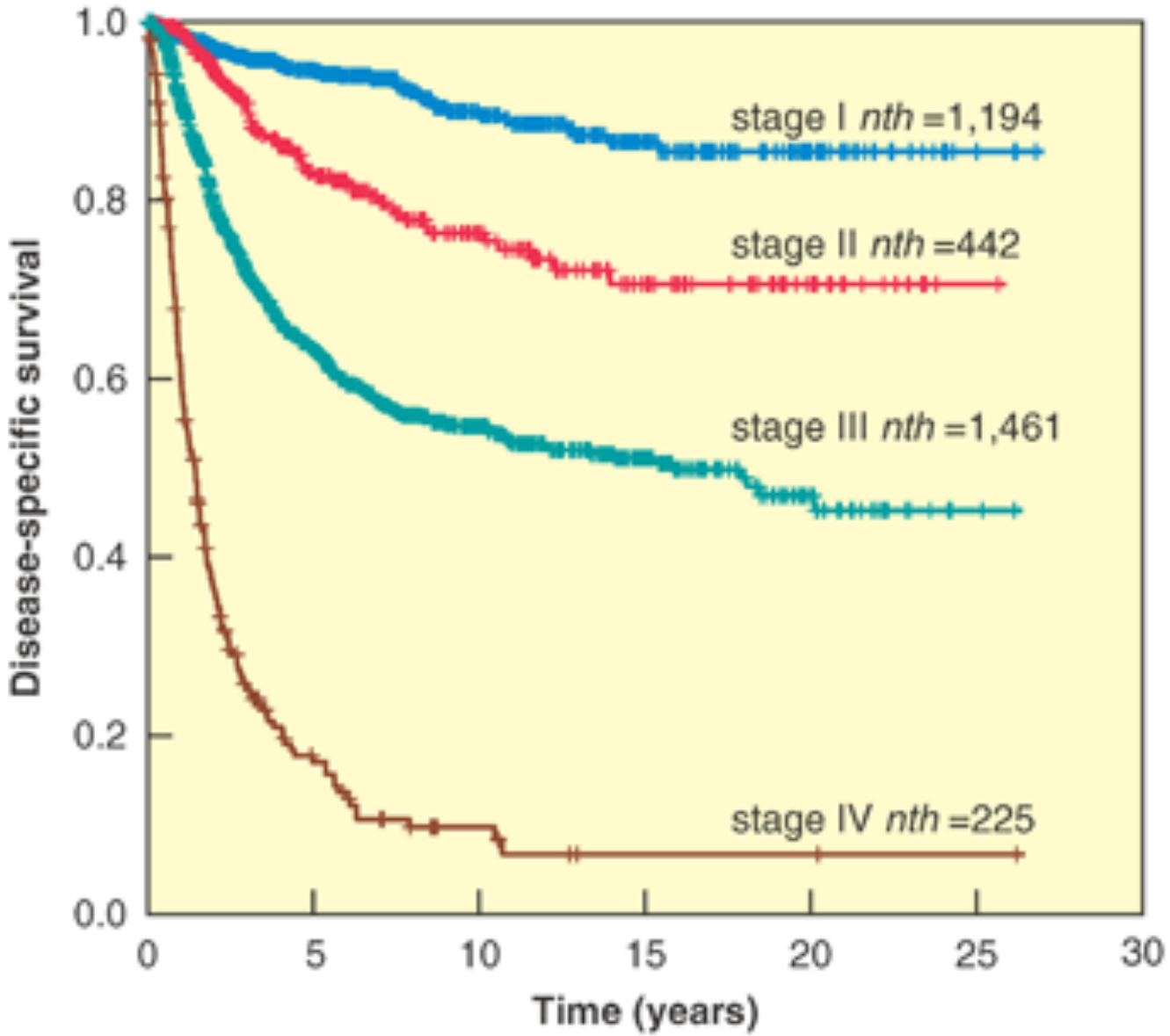


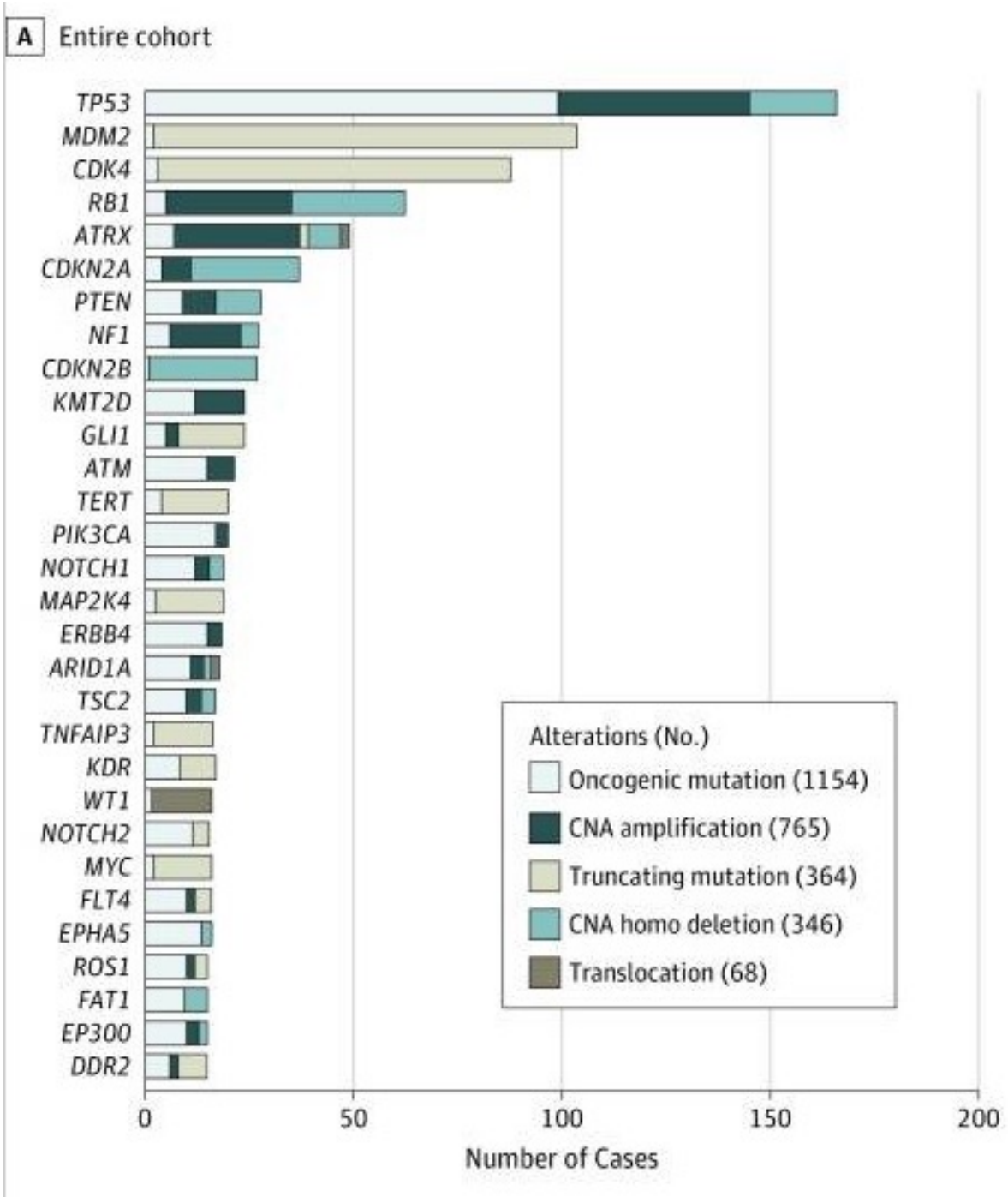
Figure 90.3 Disease-specific survival for patients with extremity soft tissue sarcoma according to the 2010 American Joint Committee on Cancer staging system. The data are for 3,322 patients seen at Memorial Sloan Kettering Cancer Center from 1982 through 2013.

Genomic alterations in STS

- Single reciprocal translocations
  - e.g., Ewing, synovial sarcoma, round cell liposarcoma
- Complex karyotypic abnormalities
  - e.g., Leiomyosarcoma, pleomorphic liposarcoma, undifferentiated pleomorphic sarcoma (UPS), angiosarcoma
- Specific oncogenic mutations or recurrent amplification
  - e.g., WD/DD Liposarcoma, epithelioid sarcoma

Genetic alterations in STS

- 584 patients
  - Complex genomics 57%
  - Translocation 25%
  - Other 19%
- Genomic alterations in 84.6%
  - Most frequent genes
    - *TP53*, *MDM2*, *CDK4*, *RB1*, *ATRX*, *CDKN2A*, *PTEN*, *NF1*, *CDKN2B*, *KMT2D*, *GLI1*, *ATM*, *TERT*, *PI3KCA*, *NOTCH1*, *MAP2K4*, *ERBB 4*, *ARID1A*, *TSC2*, and *TNFAIP3*.

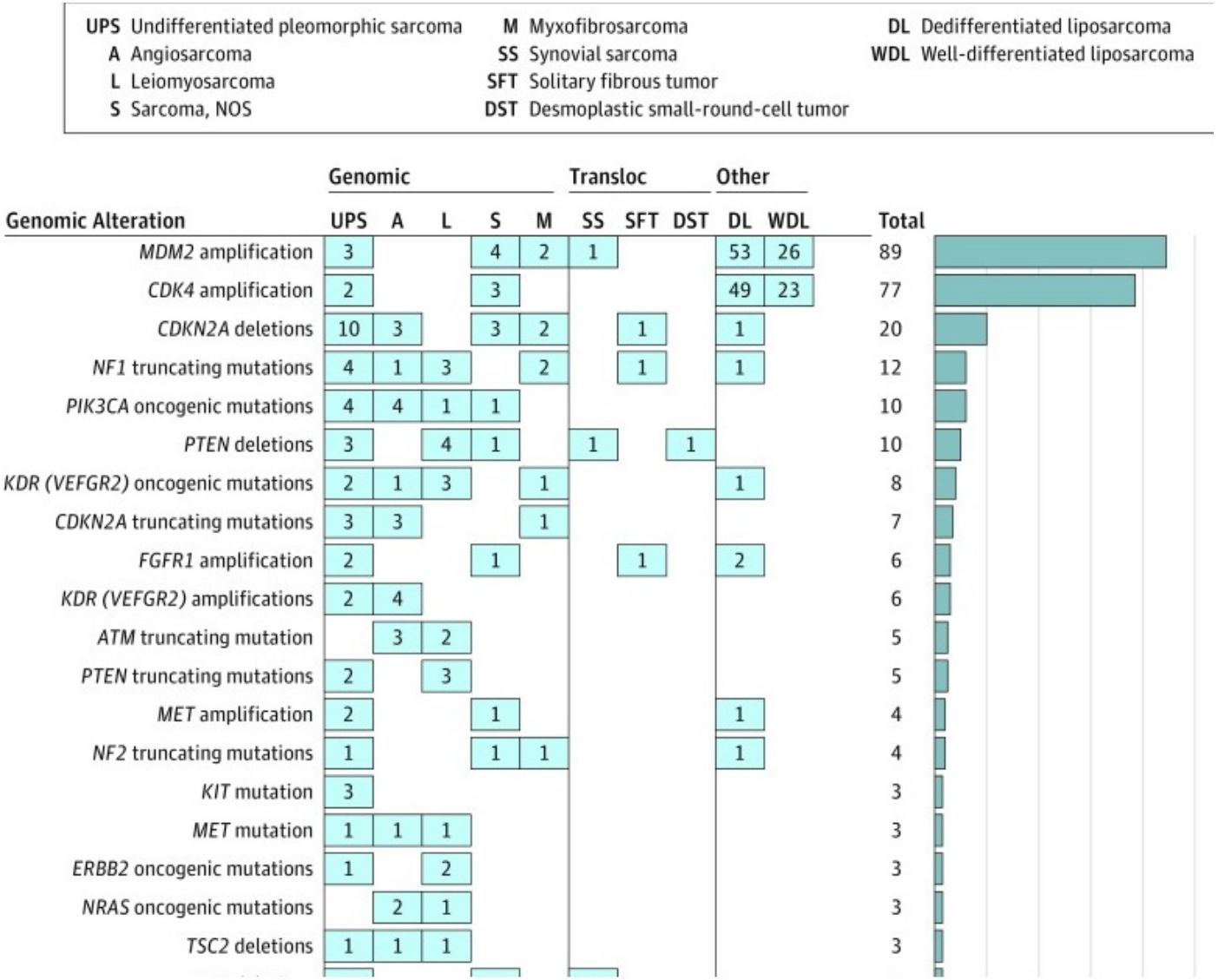


Lucchesi et al, JAMA Oncol 2018

Actionable mutations

- 29.5%

  Majority:
  - MDM2 amplification
  - CDK4 amplification



Sarcomas with reciprocal translocations

Fusion genes involving TET family		
Ewing's Sarcoma/PNET	EWS- FLI-1 (85%) -ERG (9-14%) -ETV1, ETV4, FEV (1-5%)	t(11;22) TET family RNA-binding protein (EWSR1) to ETS family transcription factor FLI-1 Overexpression : MYC, IGF-1
Desmoplastic Small Round Cell Tumor (DSRCT)	EWSR1-WT1 EWSR1-ERG	t(11;22)
Clear Cell Sarcoma	EWSR1-ATF1	t(12;22)
Extraskeletal Myxoid Chondrosarcoma	EWSR1-NR4A3	t(9;22) INI-1
Myxoid/Round Cell Liposarcoma	TLS-CHOP EWSR1-CHOP (DDIT3)	t(12;16) TET RNA binding protein to DDIT3 Overexpression: MDM2(TLS), CDK4, Met, PDGFα (EWSR1)

Sarcomas with reciprocal translocations

	Fusion genes involving chromatin remodeling genes	
Synovial Sarcoma	SS18(SYT)-SSX1; SS18(SYT)-SSX2 (monophasic)	t(X;18)
	Fusion genes involving growth factors	
Dermatofibrosarcoma protuberans (DFSP)	COL1A1-PDGFB	t(17;22) upregulates expression of PDGFR
	Fusion genes involving RTK genes	
Inflammatory Myofibroblastic tumor	TPM3-ALK	Rearrangement of ALK gene
	Other fusion genes	
Alveolar Rhabdomyosarcoma	PAX3-FHKR (FOXO1A)	t(2;13)
Alveolar soft part sarcoma	ASPSL-TFE-3	t(X;17)
Solitary fibrous tumor (SFT0	NAB2-STAT6	Inv(12)
Tenosynovial Giant Cell tumor	COL6A3-CSF1	t (1;2)

Sarcomas with specific oncogene mutations

GIST	Kit or PDGFRα	Activating mutation
Fibromatosis	APC or CTNNB1 mutation	Beta catenin pathway alteration
Perivascular epithelioid cell tumor (PEComa)		LOH of TSC1
Epithelioid sarcoma	SMARCB-1 (INI-1)	del, mutation, inactivation of INI-1
Epithelioid Hemangioendothelioma	WWTR1-CAMTA1	Activation of MAP kinase pathway

Actionable mutations

Disease	Actionable Genetic Alteration	Rx
ASPS	ASPSL-TFE-3	Cediranib, TKI
Alveolar Rhabdomyosarcoma	PAX3-FHKR (FOXO1A)	Temsirolimus + Cixutumumab
Dedifferentiated Liposarcoma	CDK4 amplification, MDM2	Palbociclib, (nutlins)
DFSP	COL1A1-PDGFB	Imatinib
Epithelioid sarcoma	INI-1 deficient	Tazemetostat
Fibromatosis	CTNNB1 or APC	Imatinib, sorafenib
GIST	C-kit PDGFRA D842V Mutation	Imatinib Avapritinib
IMF	TPM3-ALK	Crizotinib, Ceritinib
NTRK fusion sarcomas	NTRK	Larotrectinib
PEComa	LOH TSC1	mTOR inhibitor (sirolimus, everolimus)
Solitary fibrous tumor (SFT)	NAB2-STAT6	VEGF TKI, sunitinib
Tenosynovial Giant Cell tumor	COL6A3-CSF1	Pexidartinib

NTRK gene fusions have a high incidence in sarcoma

- *NTRK* genes (NTRK1, NTRK2 or NTRK3) encode the TRK receptors (TRKA , TRKB and TRKC, respectively)[1,2]
- There is a high incidence of *NTRK* gene fusions in both paediatric and adult sarcomas[1,3]
  - Around ¼ of adult *NTRK* gene fusions positive tumours are sarcomas[2]

TUMOURS CLASSIFICATION BY *NTRK* GENE FUSIONS[2]

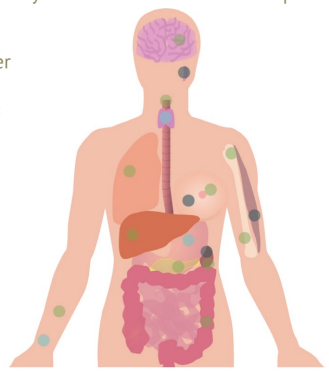
Cancers enriched for TRK fusions

Frequency >90%
- MASC
- Cellular and mixed congenital mesoblastic nephroma
- Secretory breast carcinoma
- Infantile fibrosarcoma

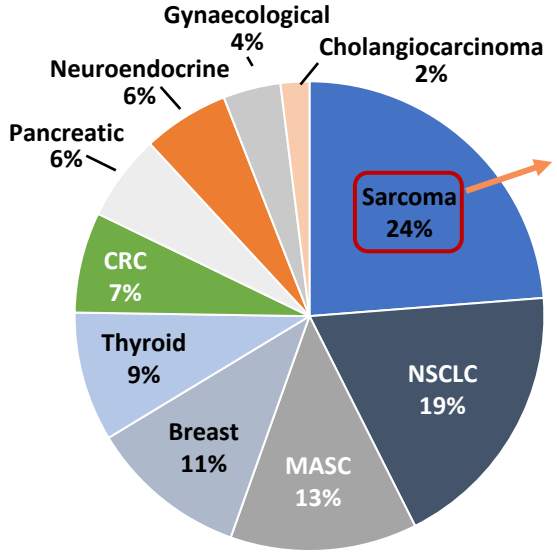
Cancers harbouring TRK fusions at lower frequencies

Frequency 5% to 25%
- Gastrointestinal stromal tumour (pan-negative)
- Spitzoid tumours
- Thyroid cancer

Frequency <5%
- Acute lymphoblastic leukaemia, acute myeloid leukaemia, histiocytosis, multiple myeloma and dendritic cell neoplasms
- Breast cancer
- Cholangiocarcinoma
- Head and neck cancer
- Pancreatic cancer
- Renal cell carcinoma
- Sarcoma
- Colorectal cancer
- High-grade glioma
- Lung cancer
- Melanoma
- Sarcoma



INCIDENCE OF *NTRK* GENE FUSIONS IN SARCOMA[3]



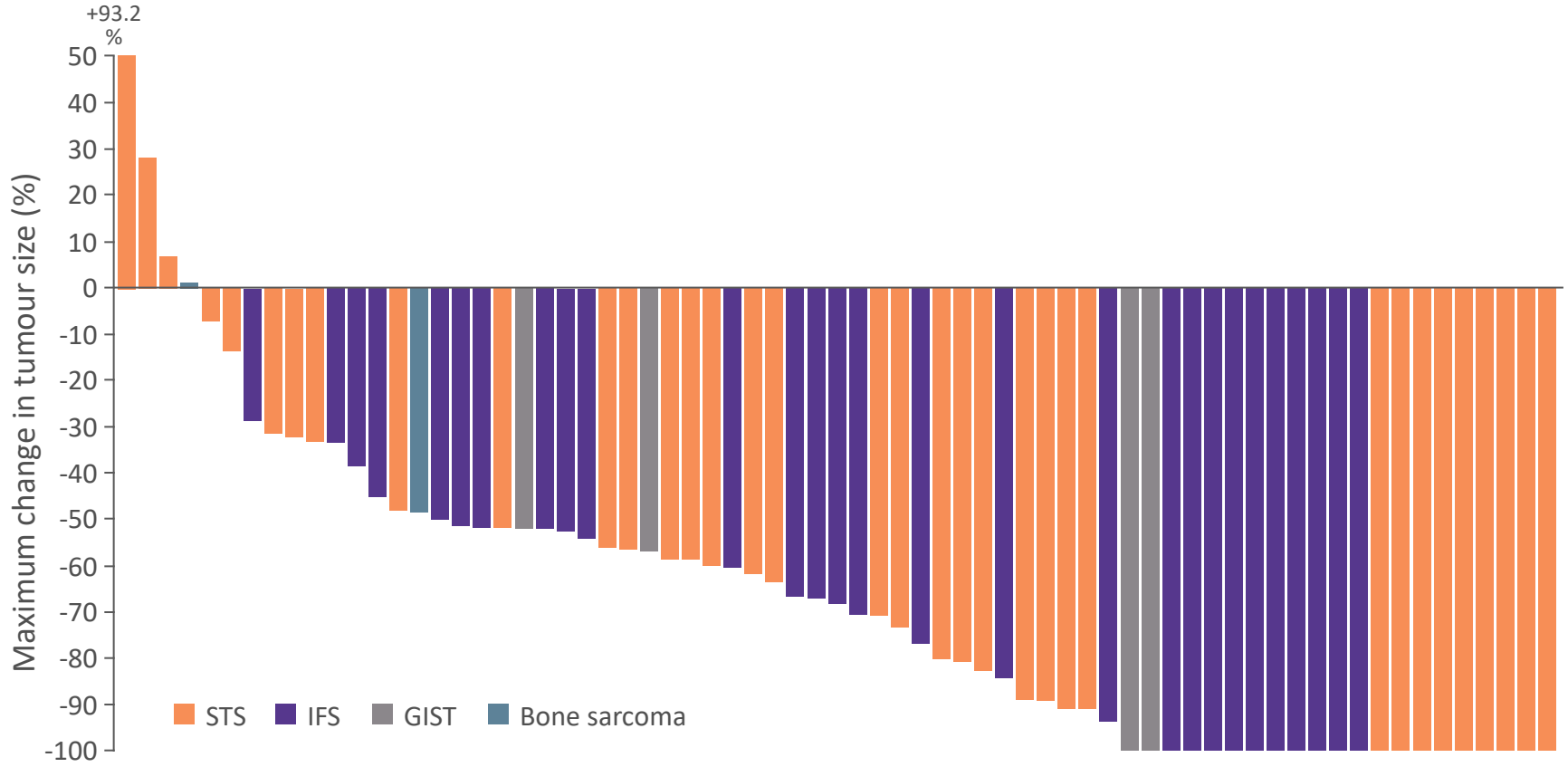
- **Sarcoma NOS, n=7**
- Cervical adenosarcoma, n=1
- Dedifferentiated chondrosarcoma, n=1
- Endometrial stromal sarcoma, n=1
- Follicular dendritic cell sarcoma, n=1
- GIST, n=1
- MPNST, n=1

CRC, colorectal cancer; GIST, gastrointestinal stromal tumour; NOS, not otherwise specified; MASC, mammary analogue secretory carcinoma; MPNST, malignant peripheral nerve sheath tumour; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic tropomyosin-related kinase; TRK, tropomyosin receptor kinase

1. Cocco, et al. Nat Rev Clin Oncol 2018;15:731–47; 2. NTRK CONNECT BluePrint. Available from: https://ntrkconnect.info/ntrk-gene-fusions-trk-inhibitors-and-testing-approaches-blueprint/. Accessed March 2020; 3. Doebele, et al. Lancet Oncology 21:271-282; 21:271–82

TRK-INHIBITION PROVIDES ROBUST RESPONSES IN PATIENTS WITH *NTRK* GENE FUSION-POSITIVE SARCOMA

EFFICACY OF LAROTRECTINIB IN SARCOMAS HARBOURING TRK FUSIONS: BEST CHANGE IN TARGET LESIONS



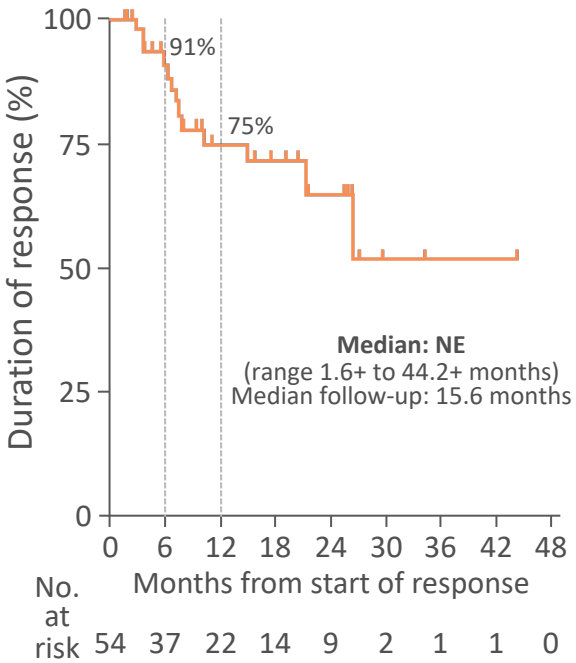
Data cut-off: Feb 19, 2019

IFS, infantile fibrosarcoma; *NTRK*, neurotrophic tropomyosin receptor kinase; STS, soft tissue sarcoma; TRK, tropomyosin receptor kinase; GIST, gastrointestinal stromal tumour

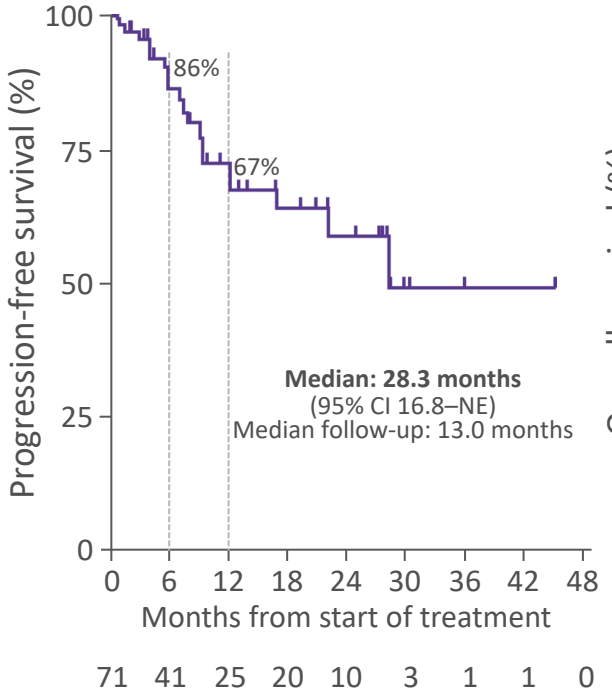
Demetri GD, et al. CTOS 2019. Abstract #3254588

TRK-INHIBITION PROVIDES DURABLE RESPONSES IN PATIENTS WITH *NTRK* GENE FUSION-POSITIVE SARCOMA

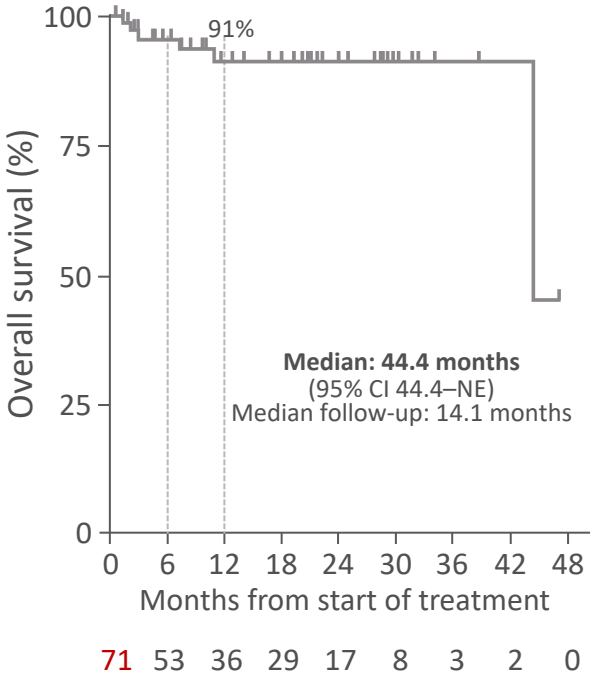
DURATION OF RESPONSE



PROGRESSION-FREE SURVIVAL



OVERALL SURVIVAL



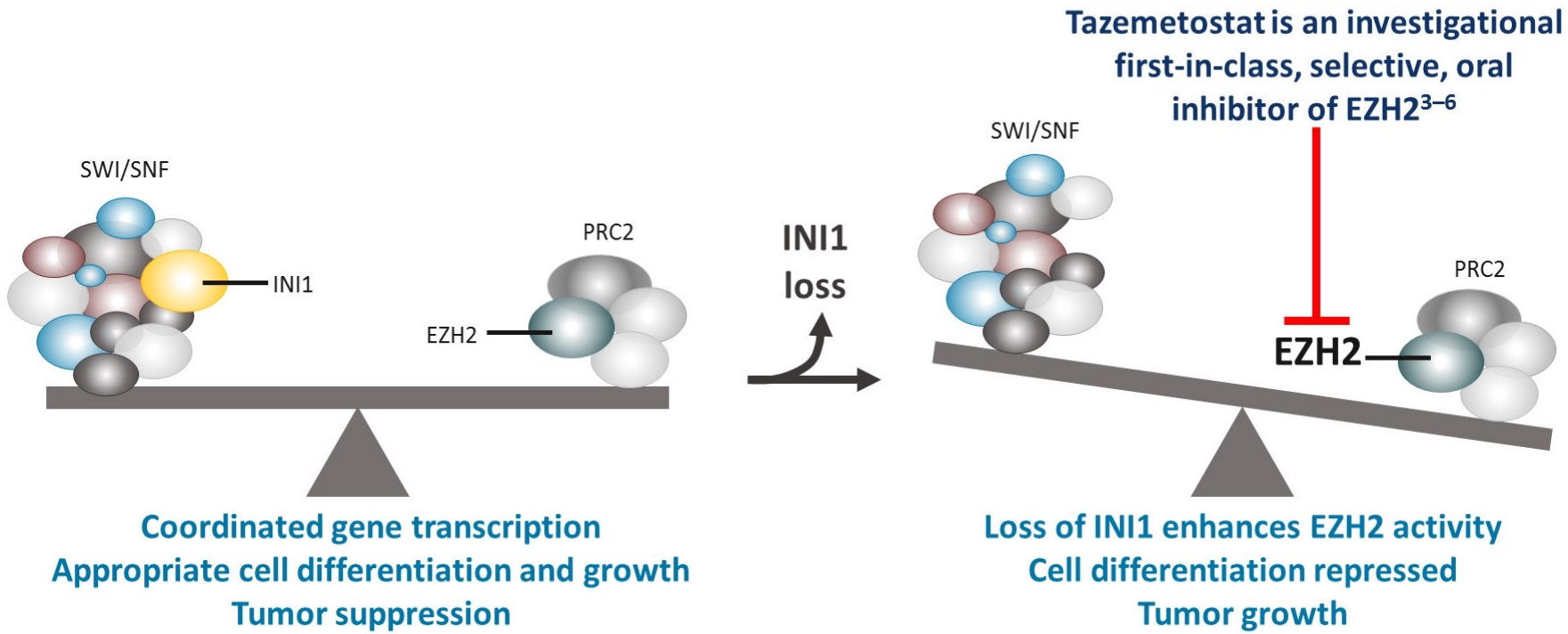
Data cut-off: Feb 19, 2019

NE, not estimable; NTRK, neurotrophic tropomyosin receptor kinase; TRK, tropomyosin receptor kinase

Demetri GD, et al. CTOS 2019. Abstract #3254588

BACKGROUND

LOSS OF INI1 CREATES AN ONCOGENIC DEPENDENCY ON ENHANCER OF ZESTE HOMOLOG 2 (EZH2)



LOSS OF INI1 CREATES AN ONCOGENIC DEPENDENCY ON ENHANCER OF ZESTE HOMOLOG 2 (EZH2)

	Histology	#pts	PR	SD	CBR	
Tazemetostat 800 mg po BID	Epithelioid sarcoma > 90% INI-1(-)	62	9 (15%); No prior Rx 6 (24%)	35	71%	selective inhibitor of EZH2 Phase II: 51% pts with tumor regression, mPFS 23.7 wk: no prior Rx 42.1 wk; (c/w doxo 12wk) DOR NR (34.1wks –NE)

GIST

	# Pts	PFS at 12	CR/PR	SD	CBR	Comments
Avapritinib 300/400 QD	PDGFRA ex 18	43 38 D842V 5 non-D842V	3/33	5	95 %	mDOR NE AEs: Nausea/vomiting, Fatigue, Anemia, Cognitive Effects, Periorbital Edema. Diarrhea Gr 3 anemia 33%, fatigue 13%

New Agents

	Histology	# Pts	CR/PR	SD	Comments
Nab-sirolimus IV qw 2/3	PEComa	31	1/11 (39) 5 > 1 y	52%	25: mutations TSC2 (9) Responses 8/9 mPFS 10.6 m; mOS 40.8 m
Abemaciclib 200 mg po BID	DDLPS	30 50% = 1L	1 PR 3 (>10% ↓)		PFS @ 12 wks: 76% (c/w 40%) mPFS 30.4w AE gr ¾: cytopenias, diarrhea

APROMISS Trial

- Phase III trial of AL3818 (anlotinib/catequentinib) v DTIC
- Multi-targeted TKI: VEGFR, C-kit, PDGF β, FGFR1/2/3
- Second line therapy
- Randomized 2:1
- 79 pts
- PFS: 2.89 v 1.64 mos p. 0.0015
- % progression free at 4, 6, 12 mos
  - TKI: 48.1%, 42.3%, 26.9%
  - DTIC 14.8%, 11.1%, 3.7%

Epithelioid Hemangioendothelioma (EHE)

- Translocation of WWTR1 (TAZ) and CAMTA1 results in fusion protein → activation of MAP kinase pathway
- Tremetinib (MEK inhibitor) 2 mg po daily
- No. Patients: 42 F>M
- TAZ-CAMTA1
  - Positive 27; Negative 7
- AE (#pts): rash (35) fatigue (22), alopecia (12), edema (11) GI, anemia (14), hypoalbuminemia (11)
- 0 CR, 3 PR (TAZ-CAMTA1 negative), SD 40% > 6 months
- mPFS 8.2 m, OS 15 m
- QOL: decreased pain at 4 weeks

Immunotherapy and STS

Agent	ORR (%)	mPFS (m)	RR by subtype	
Ipilimumab	0	1.9	SS	Maki, 2013
Pembrolizumab	**18**	4.5	**UPS 23%** (2 CR), LPS 10%	Burgess, 2019
Atezolizumab	**42**	NR	**ASPS**	Coyne, 2018
Nivolumab	0	1.8	Uterine LMS	Ben-Ami, 2017
Nivolumab Nivolumab +Ipilimumab	5 **16**	1.7 4.1	ASPS, LMS UPS 28.6, LPS 14.3	D'Angelo, 2018
Durvalumab/Tremelimumab	**14.3**	2.8	**ASPS 50%,** chordoma 20%, AS/UPS 20%	Somaiah, 2020

ST Sarcoma histology specific response to immunotherapy

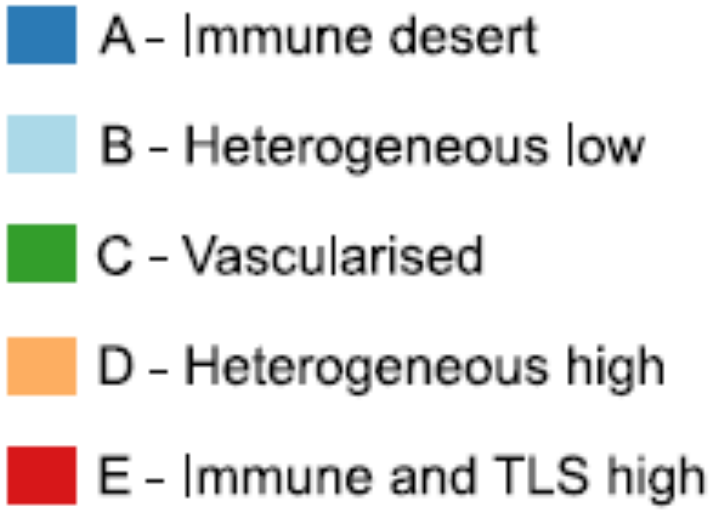
Histology	Drugs	Response Rate
UPS	Pembrolizumab Nivolumab + Ipilimumab	23% 29%
ASPS	Atezolizumab Pembrolizumab + axitinib	42% 55%
Angiosarcoma	Anti-CTLA4, Pembrolizumab, Axitinib + Pembrolizumab	71%
DDLPS	Pembrolizumab Nivolumab + ipilimumab	10% 14%
Uterine LMS	Nivolumab	0%

Tawbi et al. Lancet Oncology 2018, Chen et al. ASCO 2020, Coyne et al. CTOS 2018, Florou et al. JITC 2019, Wilky et al. Lancet Oncology 2019, Ben-Ami Cancer 2017

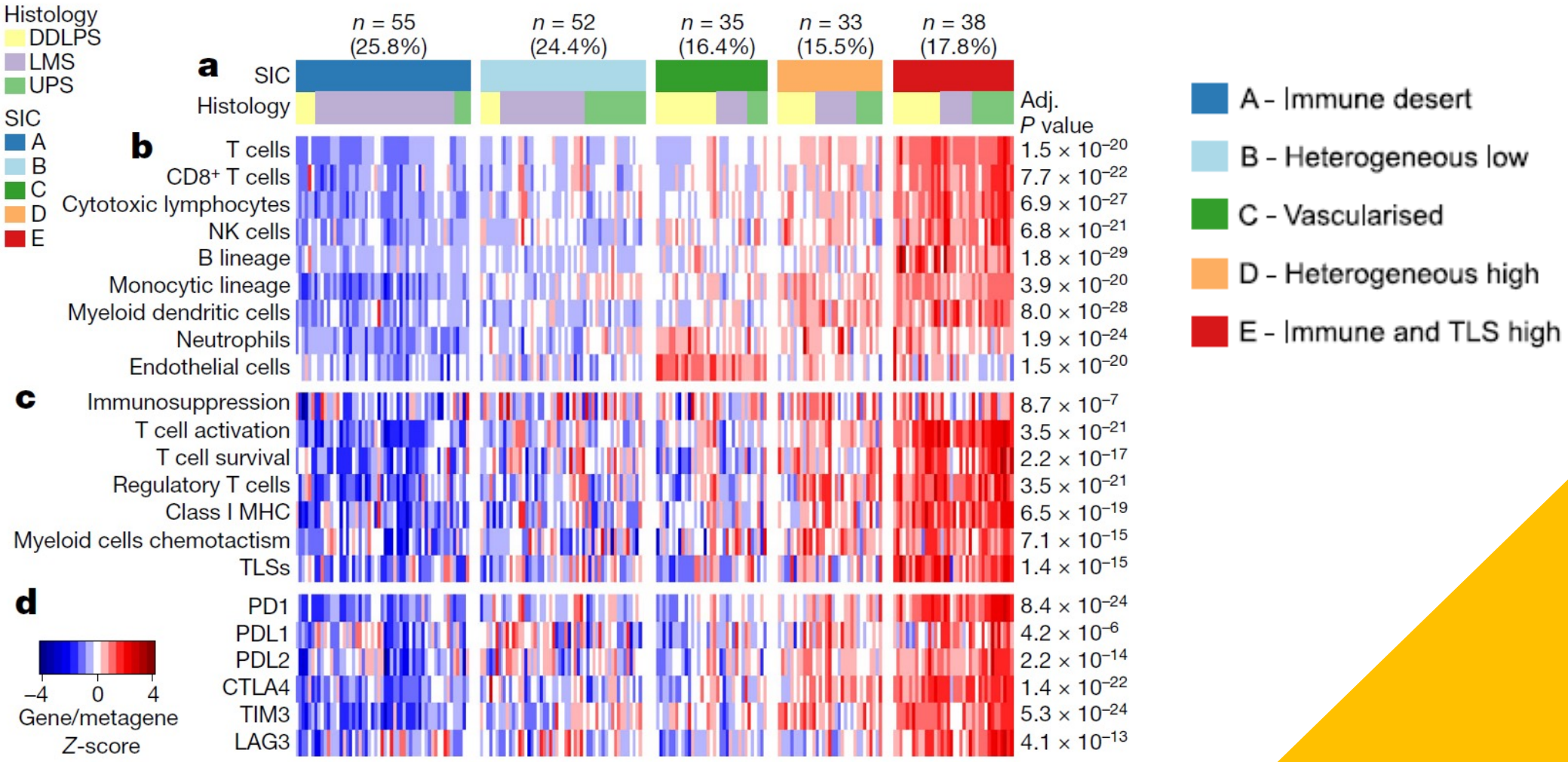
Sarcoma Immune Classification (SIC)

Petitprez, Nature, January 2020

- Gene expression profiling of 4 independent cohorts
  - Composition of tumor microenvironment (TME) by MCP counter
    - e.g., T cells, NK cells, dendritic cells, endothelial cells, B cells
  - Functional orientation of immune TME incl tertiary lymphoid structures (TLS)
  - Expression of genes related to immune checkpoints
  - Association of SIC profile with histology



Sarcoma Immune Classification (SIC)/Sarc028



Petitprez, et all Nature, 2020, 577:556

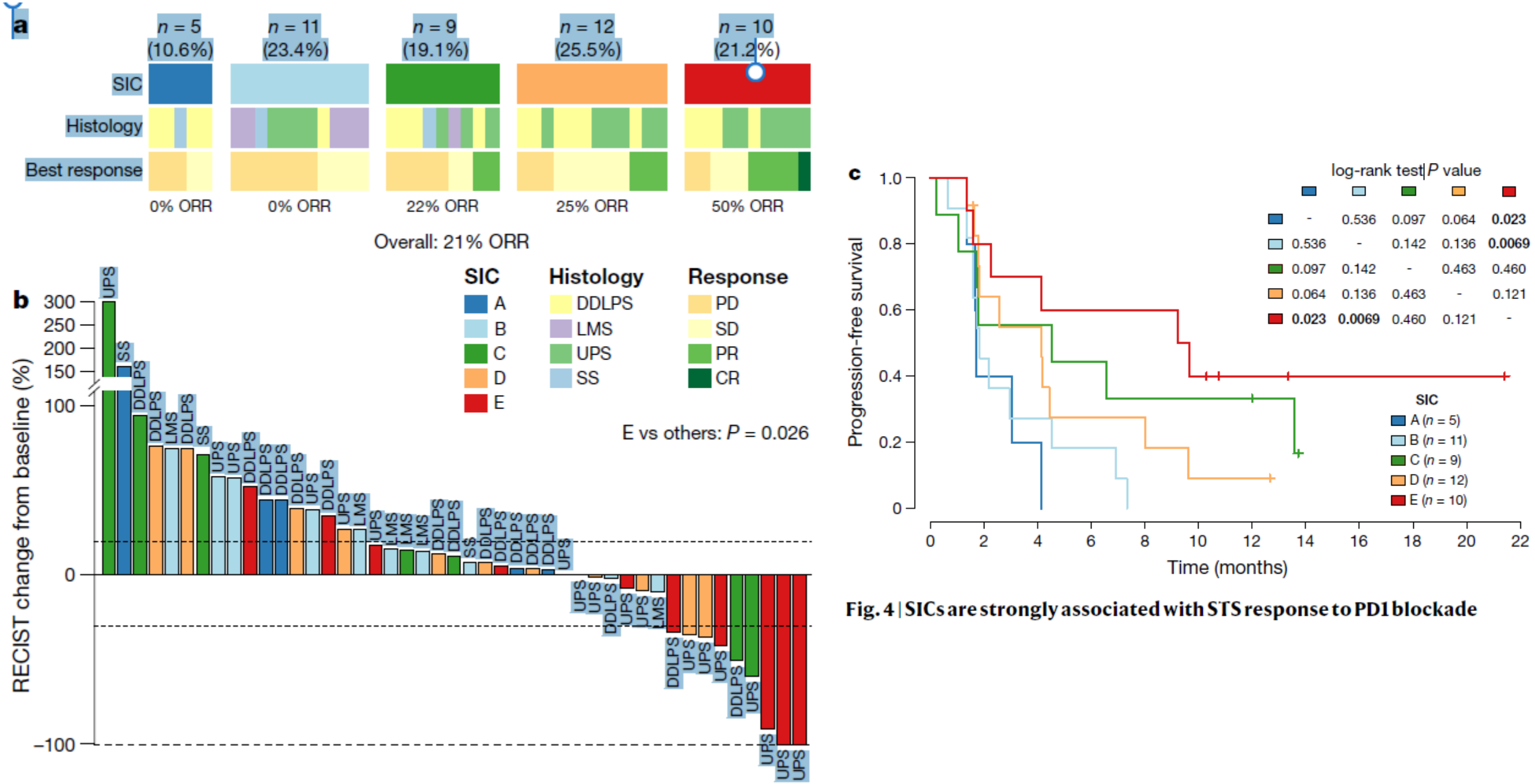


Fig. 4 | SICs are strongly associated with STS response to PD1 blockade

IO/chemo combinations

Agent	ORR (%)	mPFS (m)	RR by subtype	
Pembrolizumab	18	4.5	UPS 23% (2 CR), LPS 10%	Burgess, 2019
Pembrolizumab + Doxorubicin	22	7.8	UPS 66%, LPS 40%, LMS 30%	Pollack, 2019
Pembrolizumab + Cyclophosphamide	2	1.4	SFT	Toulmonde, 2018
Pembrolizumab + Eribulin	5.3	2.8	LMS	Nathenson, 2020
Pembrolizumab + Axitinib	25	4.7	ASPS 54.5; non-ASPS 9.5	Wilky, 2019
Nivolumab	5	1.7	ASPS, LMS	D'Angelo, 2018
Nivolumab + Sunitinib	9.3	5.9	AS, ESMC, SS, ASPS	Martin-Broto, 2019
Nivolumab + Ipilimumab + Trabectedin	22	NR	Multiple	Chawla, 2019

SPEARHEAD 1 Trial

- Sarcomas expressing MAGE-A4 in patients with HLA-A*02
- Leukapheresis collection of autologous T cells for processing: SPEAR (specific peptide enhanced affinity receptor) cells
- Afamitresgene autoleucel (Afami-cel)
- At least one prior Rx with doxo or IFOS
- 37 pts (screened > 300)
  - 32 Synovial Sarcoma
  - 5 MRC LPS
- Pretreatment with leucodepleting drug

- Response (n =25)
  - ORR 39%
    - CR 2 (SS)
  - Disease control rate (DCR) 85%
  - MDR NR, durable
- Adverse effects (> 30% pts)
  - Cytokine release syndrome 22/37
    - 95% ≤ Grade 2
  - Neutropenia
  - Lymphopenia
  - Nausea
  - Fatigue
  - Pyrexia
  - Anemia
  - Cytopenia
    - ≥ G3 at 4 weeks in 6 pts

New Immunotherapy Agents

- APX005M + Doxorubicin
  - CD40 agonist antibody, CD40 acts as a master regulator of immunity by mobilizing multiple arms of the immune system to initiate highly effective CD8 + T-cell-mediated responses against foreign pathogens and tumors.
- Lurbinectedin
  - selective inhibitor of oncogenic transcription that binds preferentially to guanines located in the GC-rich regulatory areas of DNA gene promoters. Prevents binding of transcription factors to their recognition sequences, inhibiting oncogenic transcription and leading to tumor cell apoptosis.
  - Inhibits activated transcription in tumor-associated macrophages, thereby affecting the tumor microenvironment landscape.

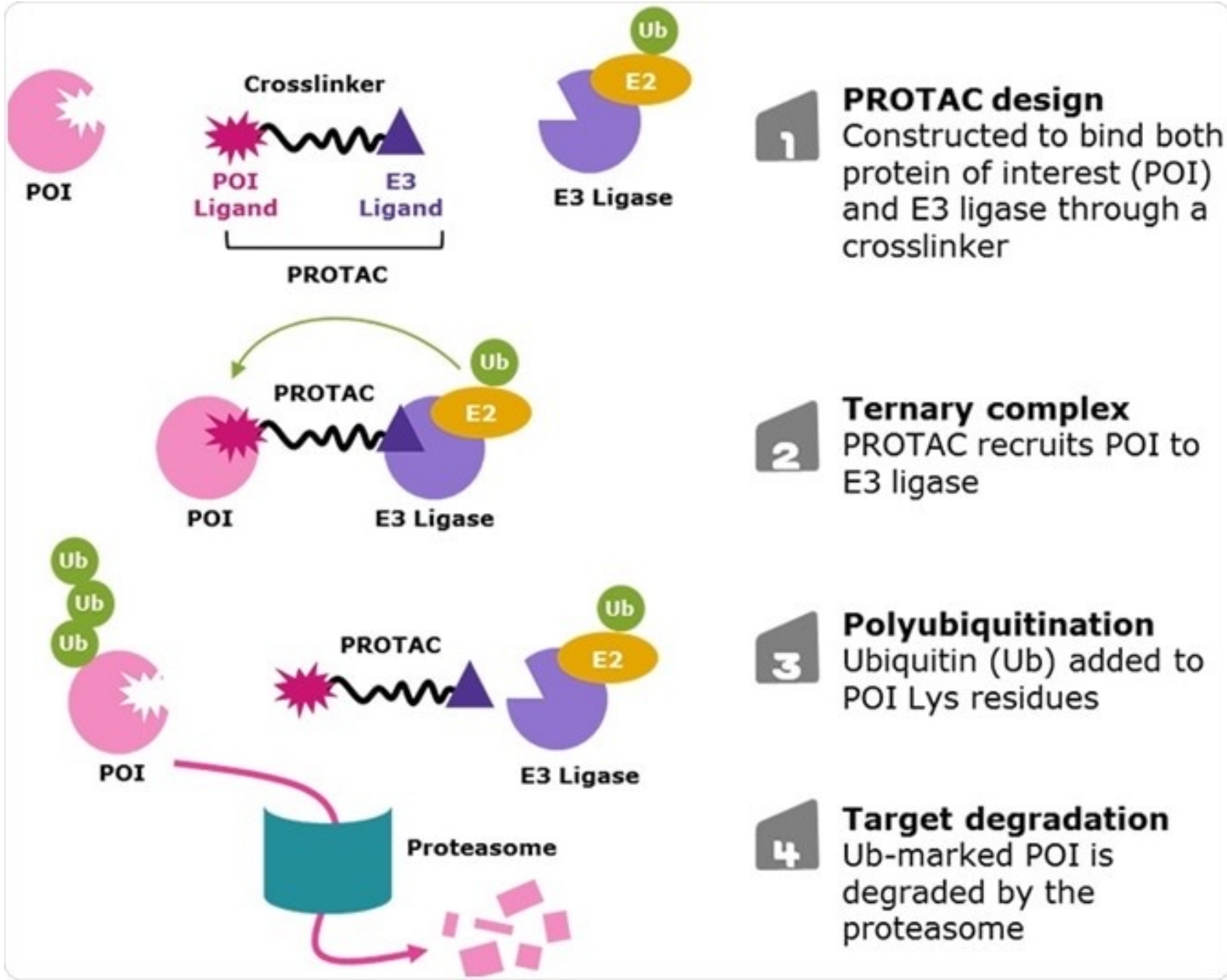
Phase I Trials

NCItrials.gov

- Sintilimab
  - anti PD-1
- AGEN1884 (Zalifrelimab)
  - anti-CTLA-4 human monoclonal antibody
- L19TNF
  - fusion protein consisting of human tumor necrosis factor (TNF)-α fused to the L19 antibody specific to the extra-domain B of fibronectin

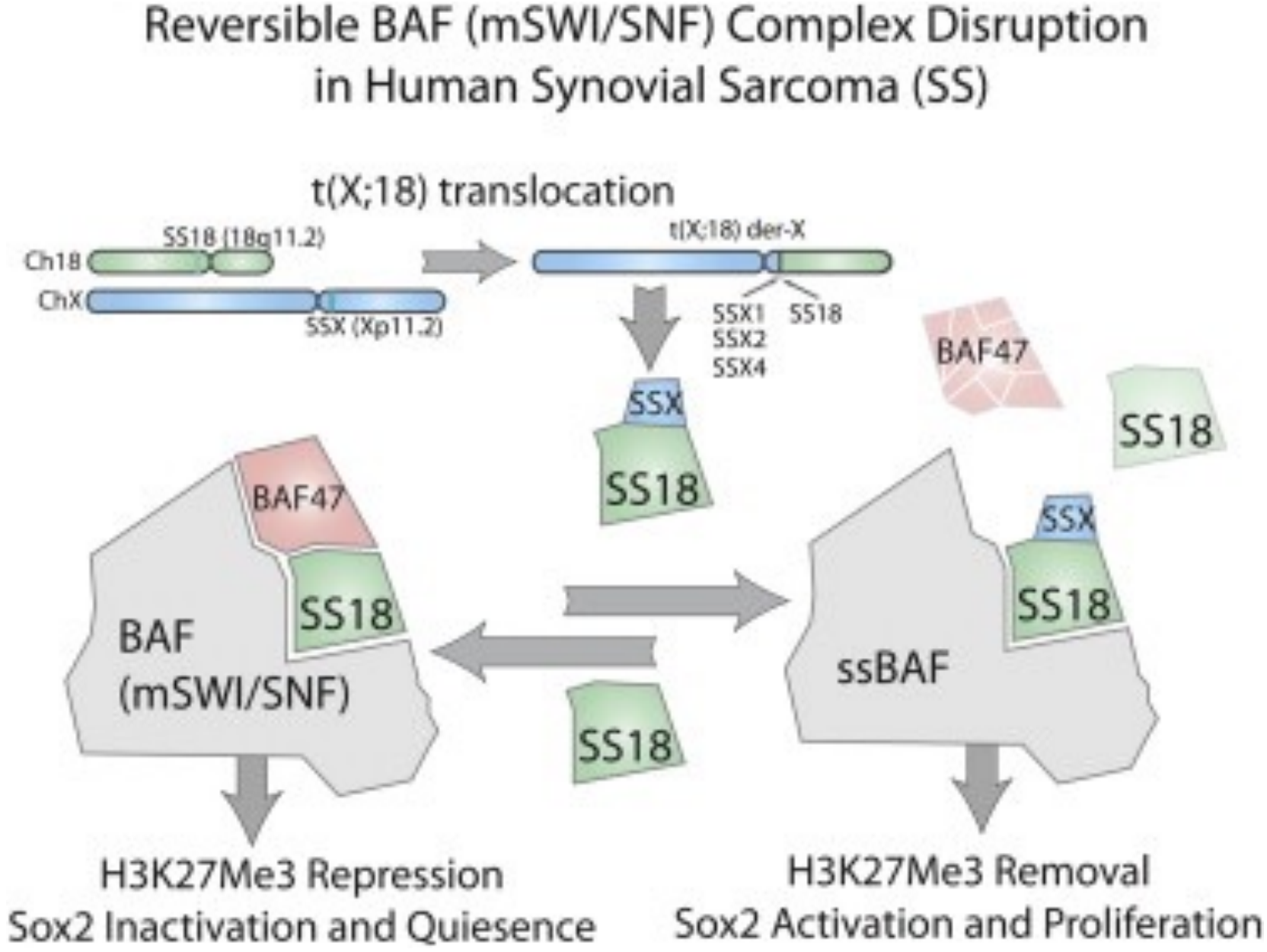
Targeted Protein Degradation (TPD)

- Strategy to target proteins with
  - active sites which are broad,
  - shallow pockets that are difficult to bridge with small molecules
  - ‘smooth’ surfaces that offer few sites for a small molecule to bind.
- Class of agents defined as proteolysis-targeting chimera (PROTAC) protein degraders
  - Heterobifunctional small molecules consisting of two ligands joined by a linker: one ligand recruits and binds a protein of interest (POI) while the other recruits and binds an E3 ubiquitin ligase, examples c-myc, kras
  - Molecular glues, promote ubiquitylation of a POI by enhancing a protein–protein interaction (PPI) between a ligase and a potential substrate


Crosslinker
POI
POI Ligand
E3 Ligand
PROTAC
Ub
E2
E3 Ligase
1
PROTAC design
Constructed to bind both protein of interest (POI) and E3 ligase through a crosslinker
PROTAC
Ub
E2
POI
E3 Ligase
2
Ternary complex
PROTAC recruits POI to E3 ligase
Ub
Ub
Ub
POI
PROTAC
Ub
E2
E3 Ligase
3
Polyubiquitination
Ubiquitin (Ub) added to POI Lys residues
Proteasome
4
Target degradation
Ub-marked POI is degraded by the proteasome

Phase I FHD-609

- Protein degrader
- Target: BRD9 component SWI-SNF complex



Summary

- “Soft tissue sarcomas” represent a heterogenous population of diseases with varying genetic alterations
- Genomic profiling is critical to identify targets for effective therapy
- Only a modest percentage of sarcoma types are responsive to immunotherapy. SPEAR cell technology is intriguing but at present applies to a minority population
- At present most effective therapies involve inhibition of tyrosine kinases with small molecules
- Emerging protein degradation technology offers possibility to target sarcomas with defined genetic alterations which at present are considered undruggable