SARCOMA UPDATES

John Charlson, MD
Associate Professor of Medicine
Hematology/Oncology
Medical College of Wisconsin

11th Annual Hematology-Oncology Symposium - October 2022

knowledge changing life

MEDICAL COLLEGE OF WISCONSIN

DISCLOSURES

- Deciphera – educational program development, consulting fee
- Adaptimmune – advisory board, consulting fee
- Ayala - DSMC

OBJECTIVES

- Understand the data that informs decision-making re: chemotherapy for localized extremity soft tissue sarcoma.
- Update knowledge of the current immunotherapy options for sarcoma treatment.
- Appreciate the various options for treatment of desmoid tumors.
- Familiarize with approved 4th line therapy for metastatic GIST.

EPIDEMIOLOGY

- Sarcoma (bone and soft tissue) – 17,000 cases/year US
  - Breast cancer – 260,000 cases/year US

- <1% of adult cancer cases; 12% of pediatric cancers (osteosarcoma, RMS, Ewing)

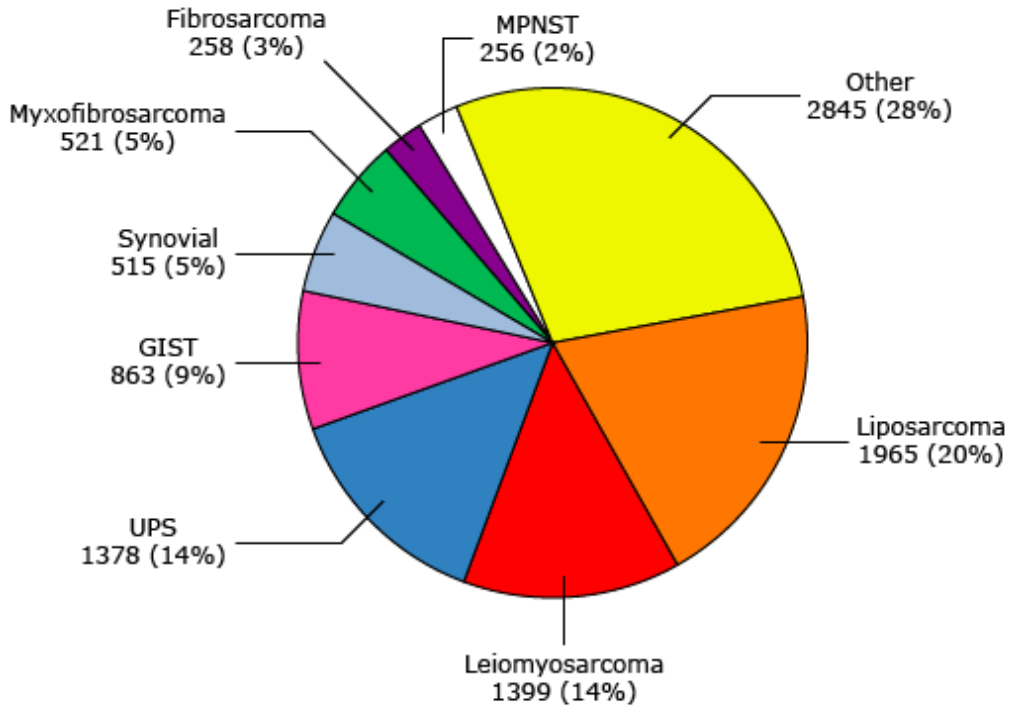
- Risk factors
  - Hereditary approx. 10% - germline TP53 approx. 3%
    - Genetic referral - <46 y/o w/STS, osteosarcoma; FamHx STS, osteo, Br Ca, CNS tumor, adrenocortical Ca in 1st or 2nd degree relative before age 50; Multiple cancers
  - Prior RT
  - Lymphedema (angiosarcoma)
  - HHV-8 (Kaposi's sarcoma) in immunosuppressed
  - Dioxins, phenoxyacetic acid herbicides (agent orange) – mixed data

Ballinger, Lancet Oncol 2016
Mitchell, PLoS One 2013

Common Sites of Soft Tissue Sarcomas

- Head & neck 9%
- Torso 18%
- Upper extremity 13%
- Retroperitoneum 13%
- Thigh, buttock, and groin 46%

Distribution of histologic subtypes in a modern database series of 10,000 adult soft tissue sarcomas, Memorial Sloan Kettering Cancer Center (MSKCC)



Distribution by histology for adult patients with soft tissue sarcoma, all sites. MSKCC 7/1/1982-5/31/2013 n = 10,000.

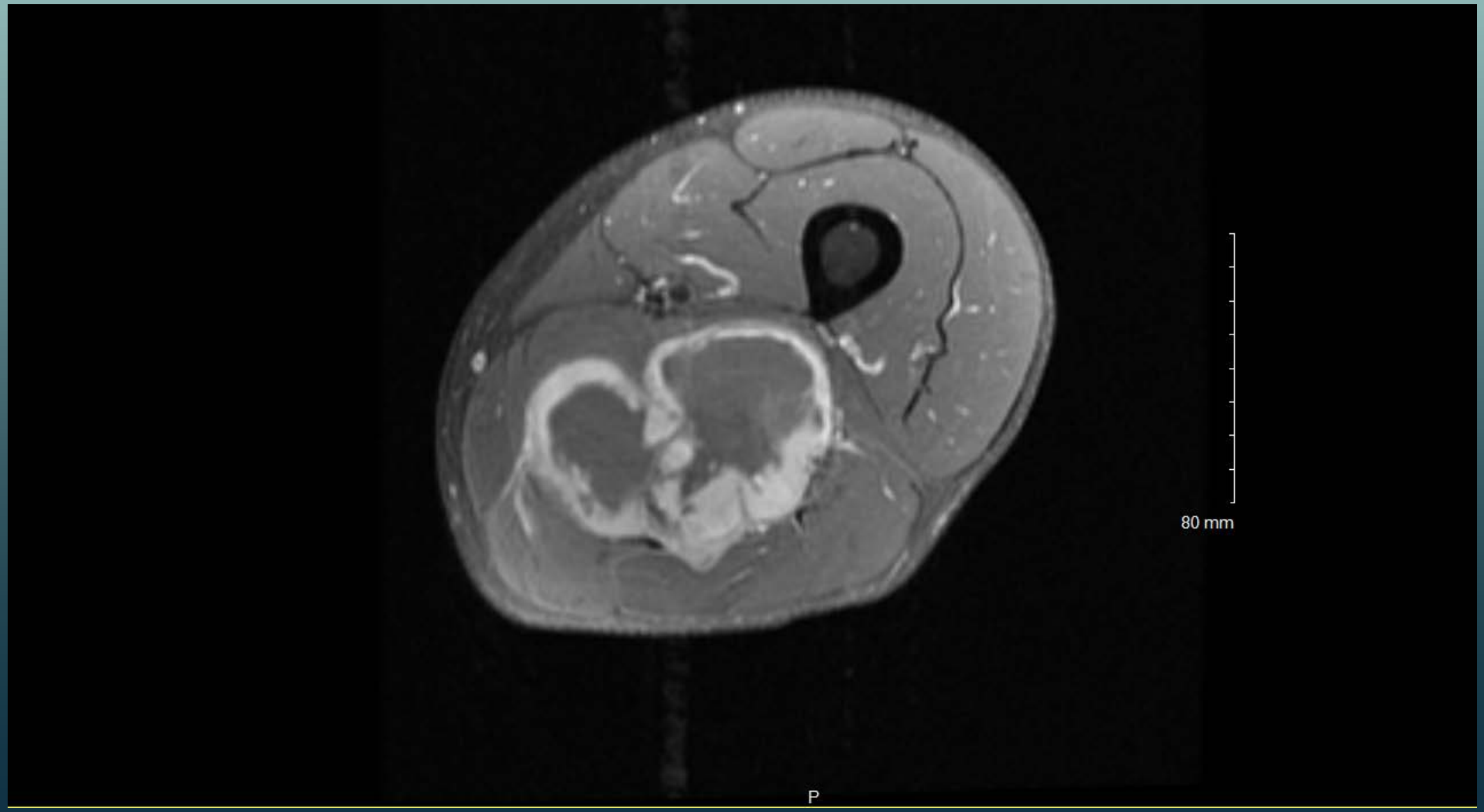
MPNST: malignant peripheral nerve sheath tumor; GIST: gastrointestinal stromal tumor; UPS: undifferentiated pleomorphic sarcoma.

Case

- 32 year old male presents with swelling of thigh for 3-4 months, has gotten larger, more uncomfortable in the past month.
- Initially attributed it to working out, wonders if hematoma?
- Sees his primary care physician
- Ultrasound – solid mass

- Next step?

Soft tissue mass, thigh



Case (continued)

- MRI – large (12cm), enhancing mass, with central necrosis
- Suspicious for sarcoma

- Next step?

DIAGNOSIS and STAGING - STS

- Biopsy
  - Core needle, imaging guidance
  - Incisional – if more tissue needed
  - Both should be planned under direction of surgeon

- Imaging
  - MRI – extremity/trunk primary tumors; Myxoid liposarcoma - spine
  - CT – abd/retroperitoneum primary; Chest for lung staging – most common met site
  - PET – not standard – may differentiate neurofibroma v MPNST; WD vs DD liposarcoma

- Lymph node metastases uncommon adult type STS
  - Exceptions - **s**ynovial, **c**lear cell, **a**ngiosarcoma, **r**habdomyosarcoma, **e**pithelioid (SCARE)

Case (continued)

- Core needle biopsy, CT guided
- Pathology – high grade malignancy, some spindled and some epithelioid appearing cells.
  - Vimentin, CK, CD99 positive.
  - FISH – SS18 (SYT) translocation
  - Confirms diagnosis – Synovial Sarcoma
- CT chest/abd/pelvis – negative for metastatic disease

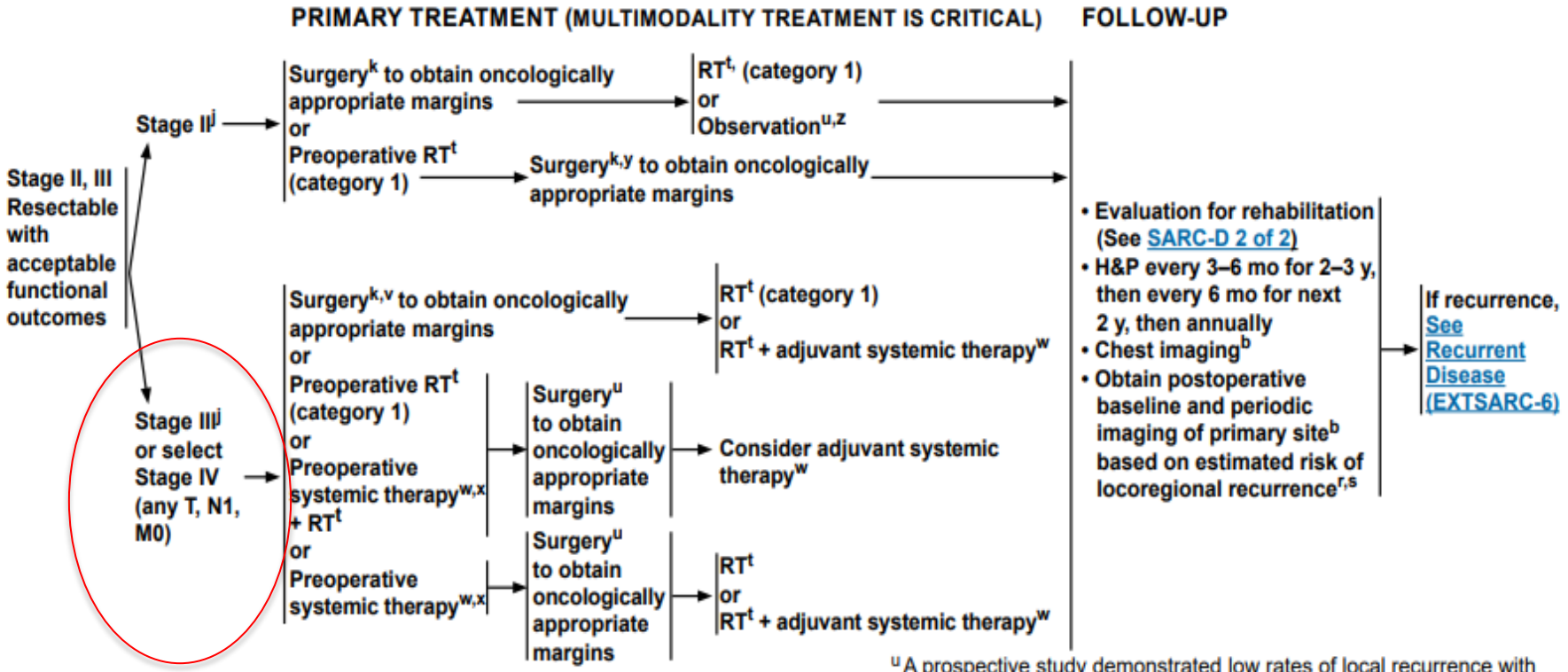
PATHOLOGY

- IHC
  - Desmin – RMS, LMS
  - MDM2 – WD/DD LPS
  - Cytokeratin – Not common in sarcoma, may see in synovial or other
  - S100 – nerve sheath or melanocytic e.g. clear cell sarcoma
- Chromosomal translocations –1/3 of sarcomas
  - Ewing sarcoma and variants
  - Synovial sarcoma, Mxyoid liposarcoma
  - Inflammatory myofibroblastic tumor (TMP3-ALK) – functional/treatment
  - FISH, or RT-PCR for protein product

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2021
Extremity/Body Wall, Head/Neck

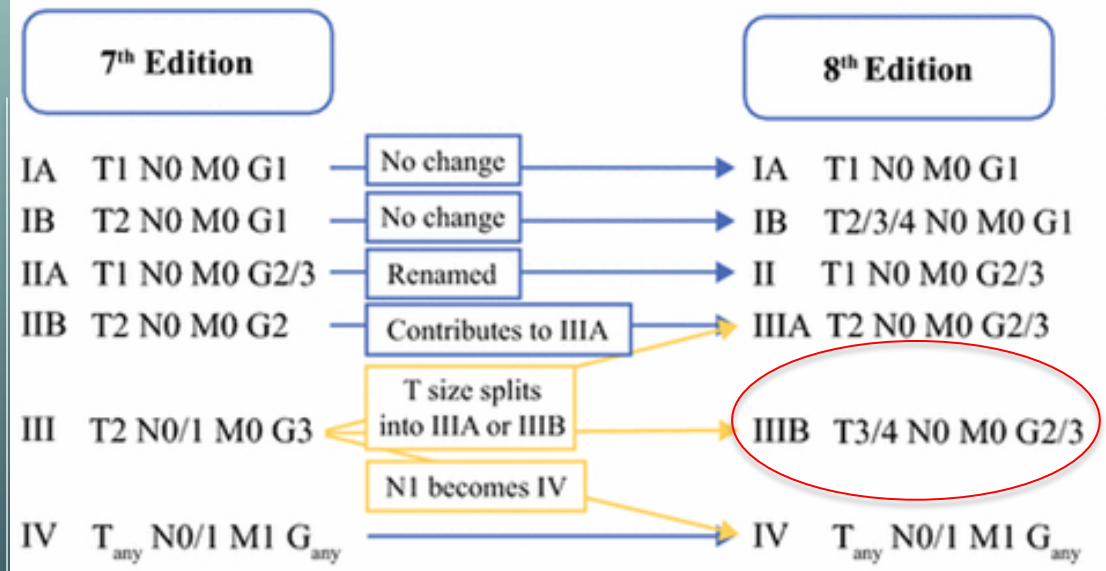
NCCN Guidelines Index
Table of Contents
Discussion



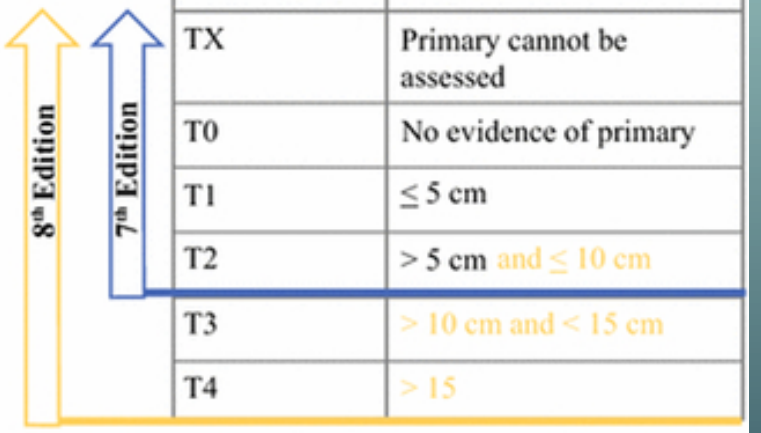
[b] See Principles of Imaging (SARC-A).
[j] See American Joint Committee on Cancer (AJCC) Staging, 8th Edition (ST-2 and ST-3).
[k] See Principles of Surgery (SARC-D).
[r] In situations where the area is easily followed by physical examination, imaging may not be required.
[s] After 10 years, the likelihood of developing a recurrence is small and follow-up should be individualized.
[t] Results of a randomized study showed a non-significant trend toward reduced late toxicities (fibrosis, edema, and joint stiffness) with preoperative compared to postoperative radiation and a significant association between these toxicities and increasing treatment field size. Because postoperative radiation fields are typically larger than preoperative fields, the panel has expressed a general preference for preoperative radiation, particularly when treatment volumes are large. (Davis AM, et al. Radiother Oncol 2005;75:48-53 and Nielsen OS, et al. Int J Radiat Oncol Biol Phys 1991;21:1595-1599.) See Principles of Radiation Therapy (SARC-E).
[u] A prospective study demonstrated low rates of local recurrence with surgery alone in carefully selected patients with high-grade tumors <5 cm (Pisters PW, et al. Ann Surg 2007;246(4):675-81). Consider omission of RT for tumors <5 cm resected with wide margins; if a repeat resection would be feasible with low morbidity in the case of a recurrence.
[v] In selected cases when margin status is uncertain, consultation with a radiation oncologist is recommended. Re-resection, if feasible, may be necessary to render margins >1.0 cm.
[w] See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma Subtypes (SARC-F).
[x] PET/CT may be useful in determining response to systemic therapy (Schuetze SM, et al. Cancer 2005;103:339-348).
[y] Re-imaging using MRI with and without contrast (preferred for extremity imaging) or CT with contrast to assess primary tumor and rule out metastatic disease. See Principles of Imaging (SARC-A).
[z] Resections with wide negative margins may be considered for observation alone if the risk of radiation is unacceptable.

Comparison 7th and 8th ed of AJCC staging STS trunk and extremities

A



B

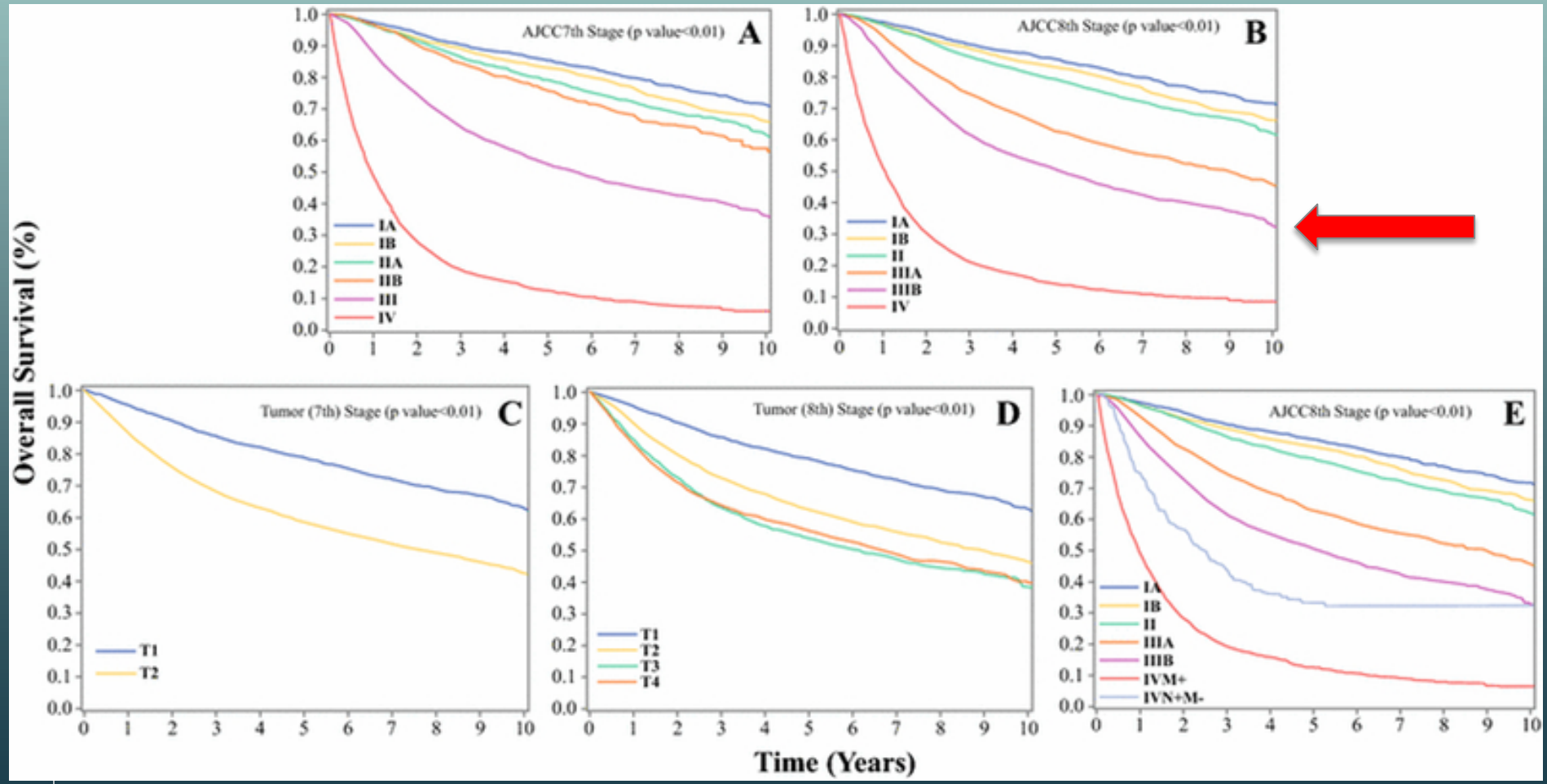


T Category	T Criteria
TX	Primary cannot be assessed
T0	No evidence of primary
T1	≤ 5 cm
T2	> 5 cm and ≤ 10 cm
T3	> 10 cm and < 15 cm
T4	> 15

C

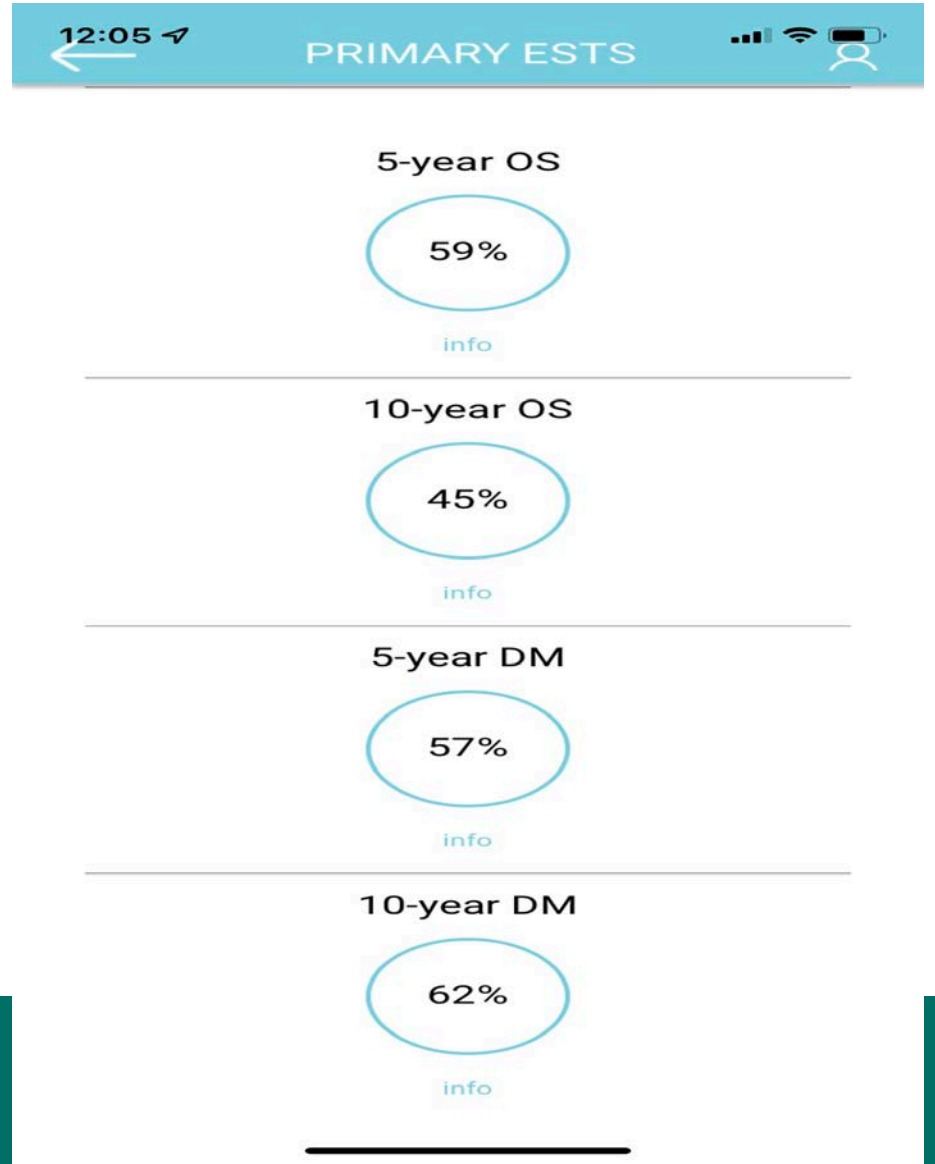
Changes in Stage between the AJCC 7th and 8th editions, n = 26,144							
AJCC 7th edition	AJCC 8th edition						
		IB	II	IIIA	IIIB	IV	Total
IA	2,976	0	0	0	0	0	2,976
IB	0	4,551	0	0	0	0	4,551
IIA	0	0	6,441	0	0	0	6,441
IIB	0	0	0	975	754	0	1,729
III	0	0	0	4,145	3,526	211	7,882
IV	0	0	0	0	0	2,565	2,565
Total	2,976	4,551	6,441	5,120	4,280	2,776	26,144

Fisher, Ann Surg Oncol 2018;25(5):126



Overall survival by stage according to the AJCC 7th edition **(A)** and 8th edition **(B)**; stratified by T stage in the AJCC 7th edition **(C)** & 8th edition **(D)**; and with the 8th edition further divided into patients with isolated nodal metastases (blue line) and distant metastases (green line) **(E)**

SARCULATOR for risk estimation



Case (continued)

- cT3N0M0, high grade, extremity, soft tissue sarcoma
- Stage 3B – estimated 5 yr OS 55%

- 62% distant mets, 55% risk of death at 10 yrs, Sarculator

- Treatment recommendations?

ADJUVANT CHEMOTHERAPY - Historical

- 2008 Meta-analysis (update) – 4 additional studies (all w/ifos) – **os significantly better w/adjuvant chemo**
  - Overall HR death 0.77 (P=0.01); ARR 6% (40 v. 46%); NNT 17 to prevent 1 death.
  - Adria/Ifos subgroup (5 studies) – HR=0.56, ARR 11% (30 v. 41).

Pervaiz etal; Cancer 2 June 2008

- EORTC 62931 – 351 pts, intermediate-high grade STS
  - Randomized – 5 cycles Adriamycin/ifosfamide vs. No chemotherapy
  - 67% extremity, 60% high grade, 40% >10cm
  - **5 year OS – 67 vs 68%**

Woll PJ et al; Lancet Oncol; epub Sept 4, 2012

MORE RECENT DATA

- Histotype-tailored chemotherapy – high-risk extremity/trunk STS
  - 5 subtypes – LMS, SS, UPS, Myxoid LPS, MPNST
  - Randomized to Epirubicin/Ifos vs. 'tailored' chemotherapy regimen, 3 cycles
  - 5-year DFS 55 vs 47%; 5-year OS 76 vs 66%
    - » Gronchi, J Clin Oncol **2020**;38(19):2178

- SARCULATOR applied to EORTC 62931 – extremity and trunk STS
  - Patients randomized to adjuvant adria-ifos vs no chemotherapy
  - Among patients with prOS <60%, chemotherapy associated with:
    - Significantly lower risk of recurrence (DFS HR = 0.49, CI 0.28-0.85)
    - Significantly lower risk of death (OS HR = 0.50, CI 0.30-0.90)
  - No difference in DFS and OS in among patients with high prOS, chemo v observation
    - » Pasquali, Eur J Can **2019**;109:51

Case (continued)

- Chemotherapy – 3 cycles, doxorubicin/ifosfamide
- Radiation therapy
- Surgery

- Pathology – 11cm tumor, 30% viable tumor, negative margins

- Follow-up

Case (continued)

- 2 years after surgery, CT chest shows multiple, new, bilateral lung nodules

- Biopsy – confirms metastatic synovial sarcoma

CHEMOSENSITIVITY - GENERALIZATIONS

- Very sensitive
  - *Round cell liposarcoma, synovial, Ewing's/PNET, rhabdomyosarcoma, angiosarcoma*
- Moderate/variable sensitivity
  - *LMS, MPNST, MFH, dediff or pleomorphic liposarc*
- Low sensitivity
  - *Fibrosarcoma, extraskeletal myxoid chondrosarcoma, epithelioid sarcoma*

METASTATIC SARCOMA – SINGLE AGENT CHEMO

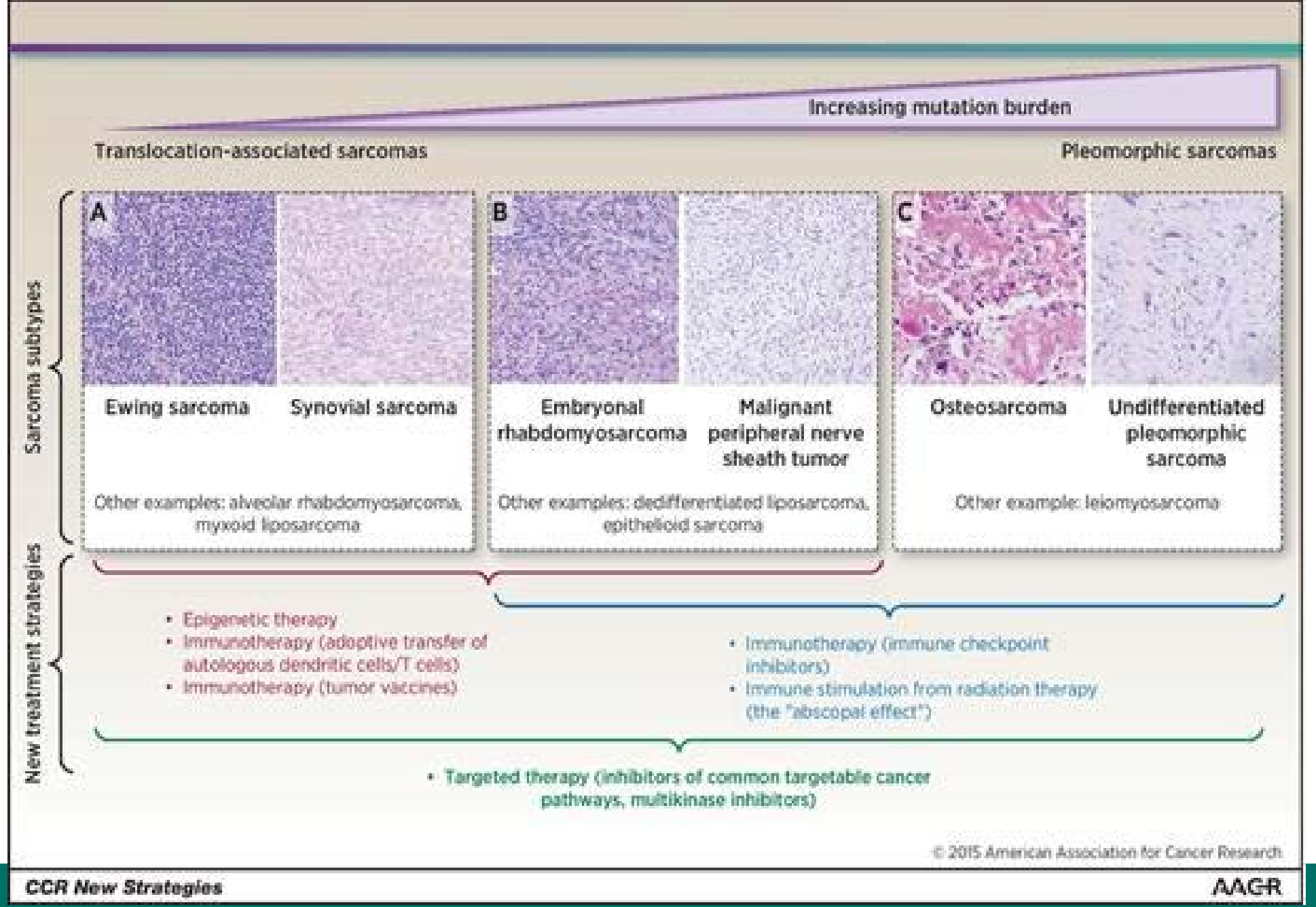
- Doxorubicin – 10-25% RR
- Pegylated liposomal doxorubicin
  - 50mg/m^2 q4w; similar efficacy to doxorubicin (Judson, Eur J Cancer. 2001;37:870.)
- Ifosfamide – dose-response,
  - e.g. MDACC study ORR 10% (6gm/m2), 21% (10gm/m2).
- Dacarbazine/Temozolomide
  - temozolomide <10%RR, disease stabilization up to 33%; PFS 2-4 mos.
- Gemcitabine
  - RR 4-18%; up to 40+% clinical benefit.
  - Fixed dose rate infusion (10mg/m2/min) seems to be more active
- Paclitaxel
  - RR around 5-10%; median PFS 2-3 mos.
  - Angiosarcoma, Kaposi's sarcoma

‘NEWER’ OPTIONS – METASTATIC STS

- **Pazopanib** – FDA approved 2012, non-adipocytic STS
  - PFS 4.6 mos, compared to 1.6 mos placebo (PALETTE study)
- **Trabectedin** – FDA approved 2015, liposarcoma and leiomyosarcoma
  - Trabectedin vs Dacarbazine, leiomyosarcoma and liposarcoma
    - PFS 4.2 vs 1.5 mos; OS similar
      - Demetri, JCO 2016
  - Myxoid liposarcoma – RR 50%; 88% 6 month PFS
    - Grosso, Lancet Oncol 2007
- **Eribulin** – FDA approved 2016, liposarcoma
  - Eribulin vs Dacarbazine, leiomyosarcoma and liposarcoma
  - Overall no difference; Liposarcoma subset – OS 15.6 vs 8.4 mos
- **Tazemetostat** (EZH2 inhibitor) – FDA approved, advanced epithelioid sarcoma (ES), 2020
  - ES – INI1/SMARCB1 loss leads to oncogenic activation of EZH2
  - ORR 15%, median PFS 5.5mos, 21% achieved 12 month PFS

Immune Checkpoint Inhibitors – Sarcoma

- Pembrolizumab
  - ORR 23% UPS, 10% dedifferentiated liposarcoma (DDLPS) (SARC 028 expansion)
- Nivolumab +/- Ipilimumab – advanced STS
  - ORR Nivo 5%; Nivo/Ipi 16% (D'Angelo, Lancet Oncol 2018)
- Doxorubicin + Pembrolizumab – metastatic sarcoma (Pollack, JAMA Oncol, 2020)
  - ORR 19%, median PFS 8.1 mos; several DDLPS and UPS pts with durable responses



Lim, Clin Cancer Res 2015;21:4753

SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA SUBTYPES[a,b,c,d]

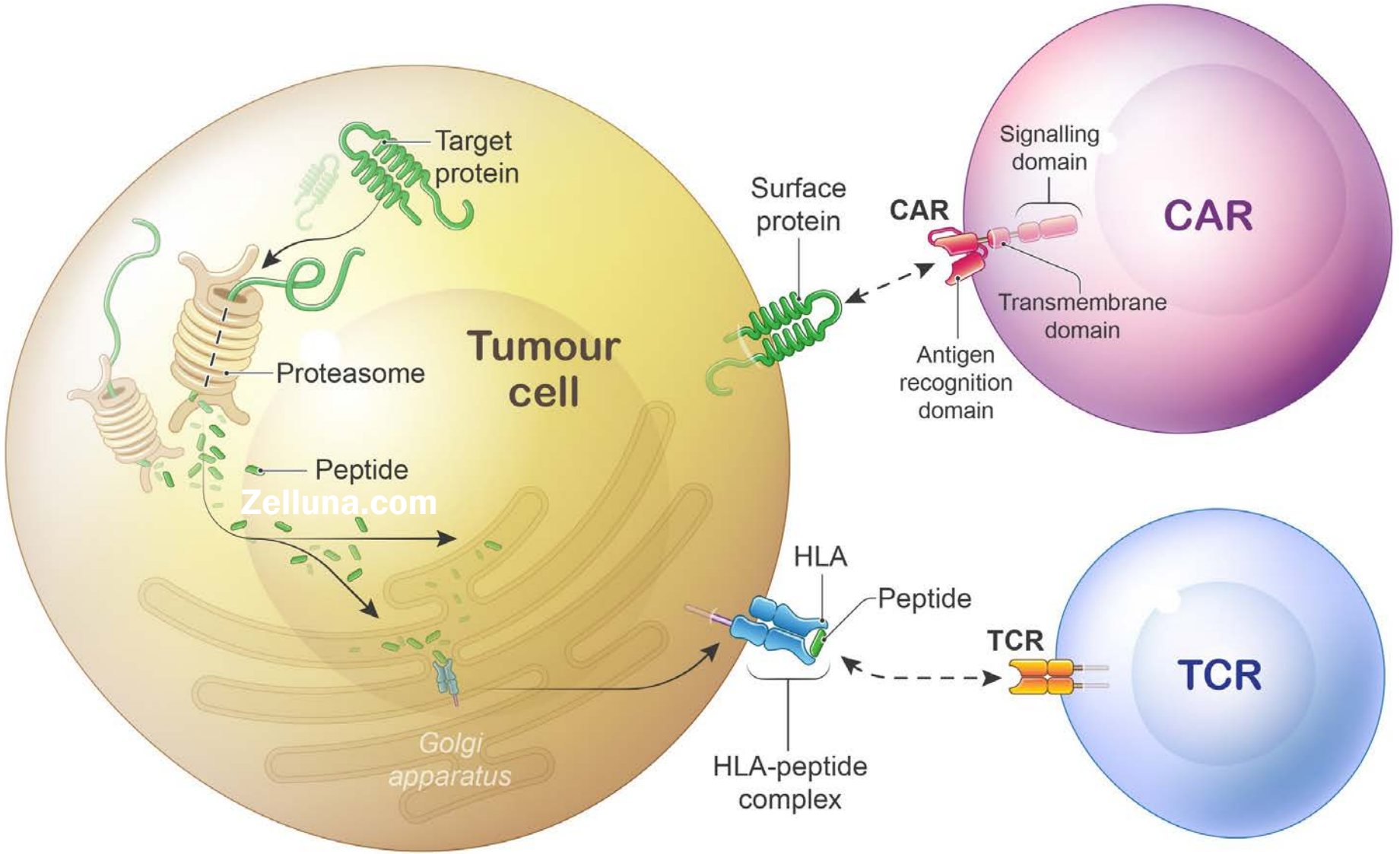
Soft Tissue Sarcoma Subtypes with Non-Specific Histologies
(Regimens Appropriate for General Soft Tissue Sarcoma[e,f]; see other sections for histology-specific recommendations)

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Neoadjuvant/ Adjuvant Therapy	• AIM (doxorubicin, ifosfamide, mesna)[1-4] • Ifosfamide, epirubicin, mesna[5]	• AD LMS only (doxorubicin, dacarbazine)[1,2,6,7] if ifosfamide is not considered appropriate • Doxorubicin[1,2,8,9] • Gemcitabine and docetaxel[10,11]	• Ifosfamide[5,9,10-14] • Trabectedin (for myxoid liposarcoma)[15]
First-Line Therapy Advanced/Metastatic	• Anthracycline-based regimens: ▸ Doxorubicin[1,2,8,9] ▸ Epirubicin[16] ▸ Liposomal doxorubicin[17] ▸ AD (doxorubicin, dacarbazine)[1,2,6,7,18] ▸ AIM (doxorubicin, ifosfamide, mesna)[1-4,8] ▸ Ifosfamide, epirubicin, mesna[5] • *NTRK* gene fusion-positive sarcomas only ▸ Larotrectinib[g,19] ▸ Entrectinib[h,20]	• Gemcitabine-based regimens: ▸ Gemcitabine ▸ Gemcitabine and docetaxel[10,11] ▸ Gemcitabine and vinorelbine[13] ▸ Gemcitabine and dacarbazine[14]	• Pazopanib[j,21] (patients ineligible for IV systemic therapy or patients who are not candidates for anthracycline-based regimens) • MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[1,2,22,23]
Subsequent Lines of Therapy for Advanced/Metastatic Disease	• Pazopanib[i,j,21] • Eribulin[i,24] (category 1 recommendation for liposarcoma, category 2A for other subtypes • Trabectedin[i,25-27] (category 1 recommendation for liposarcoma and leiomyosarcoma, category 2A for other subtypes)	• Dacarbazine[14] • Ifosfamide[5,9,10-13,28] • Temozolomide[i,29] • Vinorelbine[i,30] • Regorafenib[j,31] • Gemcitabine-based regimens (if not given previously): ▸ Gemcitabine ▸ Gemcitabine and docetaxel[10,11] ▸ Gemcitabine and vinorelbine[13] ▸ Gemcitabine and dacarbazine[14] ▸ Gemcitabine and pazopanib (category 2B)[32]	• Pembrolizumab[k,33,70] (for myxofibrosarcoma, undifferentiated pleomorphic sarcoma [UPS], cutaneous angiosarcoma, and undifferentiated sarcomas) Footnotes and references see SARC-F, 7 of 11

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Immune Checkpoint Inhibitors – Sarcoma

Subtype	Checkpoint Inhibitor	Combo	N	ORR	Median PFS (mos)	Author, date
All (bone/STS)	Pembrolizumab	None	84	18%/5%	4.5/2	Tawbi, 2017
UPS, DDLPS	Pembrolizumab	None	80 (40/40)	23% UPS 10% DDLPS	3/2	Burgess, 2019
LMS, UPS, GIST, others	Pembrolizumab	Cyclophos metronomic	50	2%	1.4	Toulmonde, 2017
All	Nivolmab +/- Ipilimumab	None	43/42	5%/16%	1.7/4.1	D'Angelo, 2018
STS	Pembrolizumab	Axitinib	36 (12 ASPS)	25%	4.7	Wilky, 2019
STS	Pembrolizumab	Doxorubicin	30	36%	5.7	Livingston, 2019
STS	Pembrolizumab	Doxorubicin	37	19%	8.1	Pollack, 2020
STS	Nivolumab	Sunitinib	68	13%	5.6	Martin-Broto, 2020
Bone	Nivolumab	Sunitinib	40	5%	3.7	Palmerini, 2020


Target protein
Proteasome
Tumour cell
Peptide
Zelluna.com
Golgi apparatus
Surface protein
CAR
Signalling domain
CAR
Transmembrane domain
Antigen recognition domain
HLA
Peptide
TCR
TCR
HLA-peptide complex

• Cellular Therapy – Synovial Sarcoma, Myxoid liposarcoma

- Endogenous T cells, genetically modified for enhanced target recognition, HLA restricted

- **Advanced synovial sarcoma, NY-ESO TCR, phase 1**
  - Majority 2+ prior therapies for metastatic disease
  - 4 Cohorts, various NY-ESO expression and lymphodepletion regimens
  - 36% ORR overall
  - High-dose fludarabine/cyclophosphamide – 50% ORR, 30 week median DOR

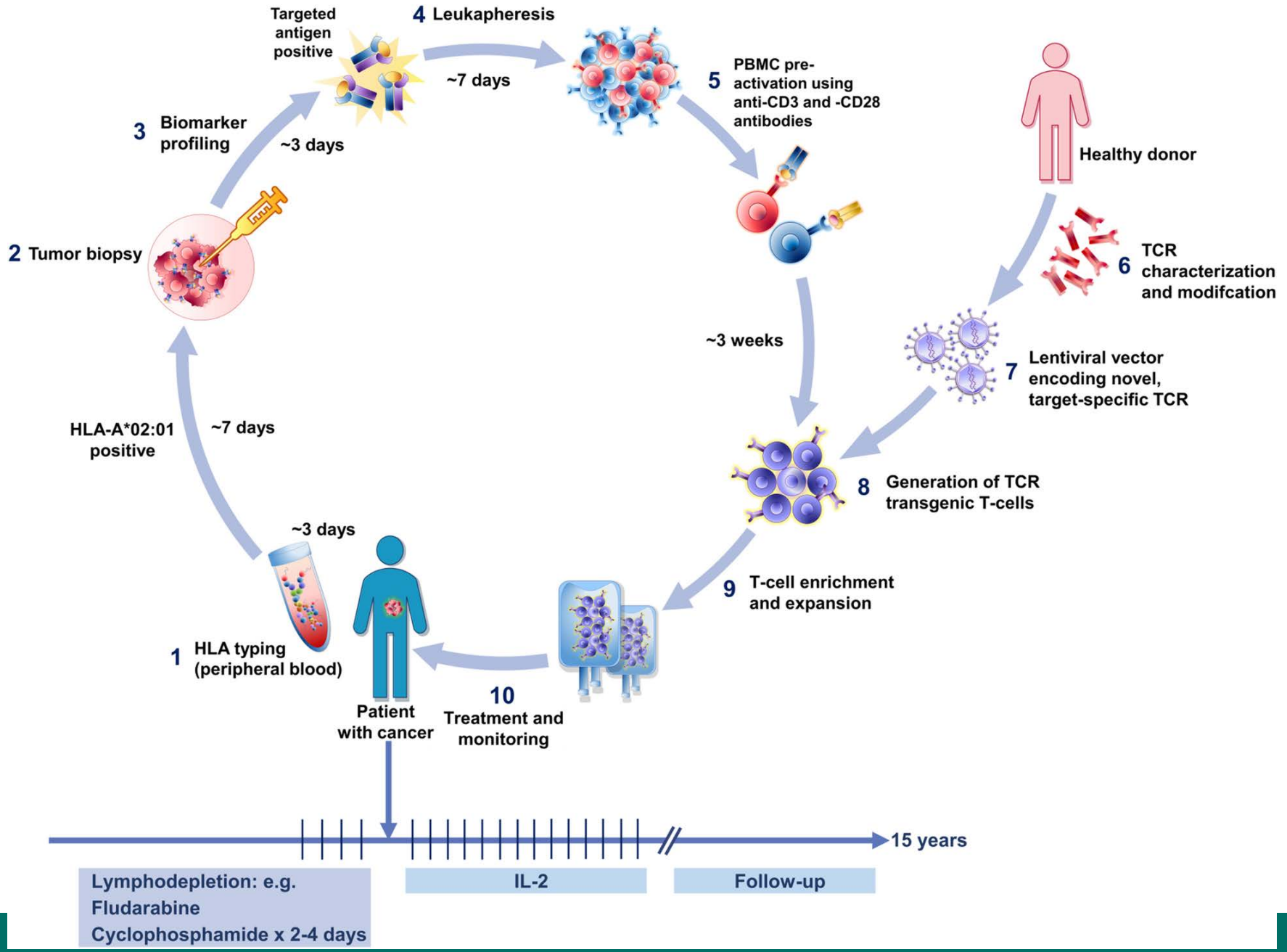
- **Advanced synovial sarcoma and MRCL, MAGE-A4 TCR, phase 2 trial**
  - 50 patients – 42 synovial sarcoma, 8 myxoid liposarcoma
  - Median 3 prior treatments for metastatic disease
  - Overall response rate 34% (36% SS, 25% MRCL)
  - Duration of response 4.3 – 65.3 weeks (75% of pts with response ongoing at time of report)

Ramachandran, J Immunother Cancer, 2019
Van Tine, CTOS Annual Meeting, 2021

TCR Trials - Sarcoma

- Spearhead-1 trial (NCT04044768) – synovial sarcoma

  - SURPASS Trial (NCT04044859) – H&N, NSCLC, urothelial
    - ADP-A2M4CD8 – CD8 coreceptor
  - SURPASS-2 - gastroesophageal


Targeted antigen positive
4 Leukapheresis
~7 days
5 PBMC pre-activation using anti-CD3 and -CD28 antibodies
Healthy donor
3 Biomarker profiling
~3 days
2 Tumor biopsy
6 TCR characterization and modifcation
~3 weeks
7 Lentiviral vector encoding novel, target-specific TCR
HLA-A*02:01 positive
~7 days
8 Generation of TCR transgenic T-cells
~3 days
9 T-cell enrichment and expansion
1 HLA typing (peripheral blood)
Patient with cancer
10 Treatment and monitoring
15 years
Lymphodepletion: e.g. Fludarabine Cyclophosphamide x 2-4 days
IL-2
Follow-up

GASTROINTESTINAL STROMAL TUMOR (GIST)

- Sites of origin
  - Stomach 40-60%, Jejunum/ileum 25-30%, duodenum 5%, colorectal 5-15%
- Risk stratification – size, mitotic rate, tumor site
- Mutation profiling
- Adjuvant therapy
  - ACOSOG Z9001 – resected GIST ≥ 3cm, Imatinib 1 year v placebo
    - 1-year RFS 98 vs 83%, favor imatinib
  - EORTC 62024 – Int/high risk GIST, 2 yrs Imatinib v placebo
    - Improved RFS; Improved time to new treatment in high risk pts
  - SSG XVIII – high risk pts, 3 years v 1 year imatinib
    - Better 10-yr RFS (53 v 42%) and OS (79 v 65%)

Approved Treatments for Advanced GIST

Medication	Line of Therapy	mPFS	ORR	Approval Yr
Imatinib[1]	1st	18.9 mos	51.4%	2001
Sunitinib[2]	2nd	5.3 mos (1.5m placebo)	7%	2006
Regorafenib[3]	3rd	4.8 mos (0.9m placebo)	4.5%	2012
Ripretinib[4]	4th	6.3 mos (1.0m placebo)	9.4%	2020
Avapritinib[5]	PDGFRA exon 18	34 mos	91%	2020

***Of note, 57% of pts treated with avapritinib in the referenced study noted cognitive effects.**

1. Gleevec Prescribing Information, Novartis, 2020
2. Demetri, Clin Can Res 2012;18:3170.
3. Demetri, Lancet 2012;381:295.
4. Blay, Lancet Oncol 2020;21:923.
5. Jones, Eur J Can 2021;145:132.

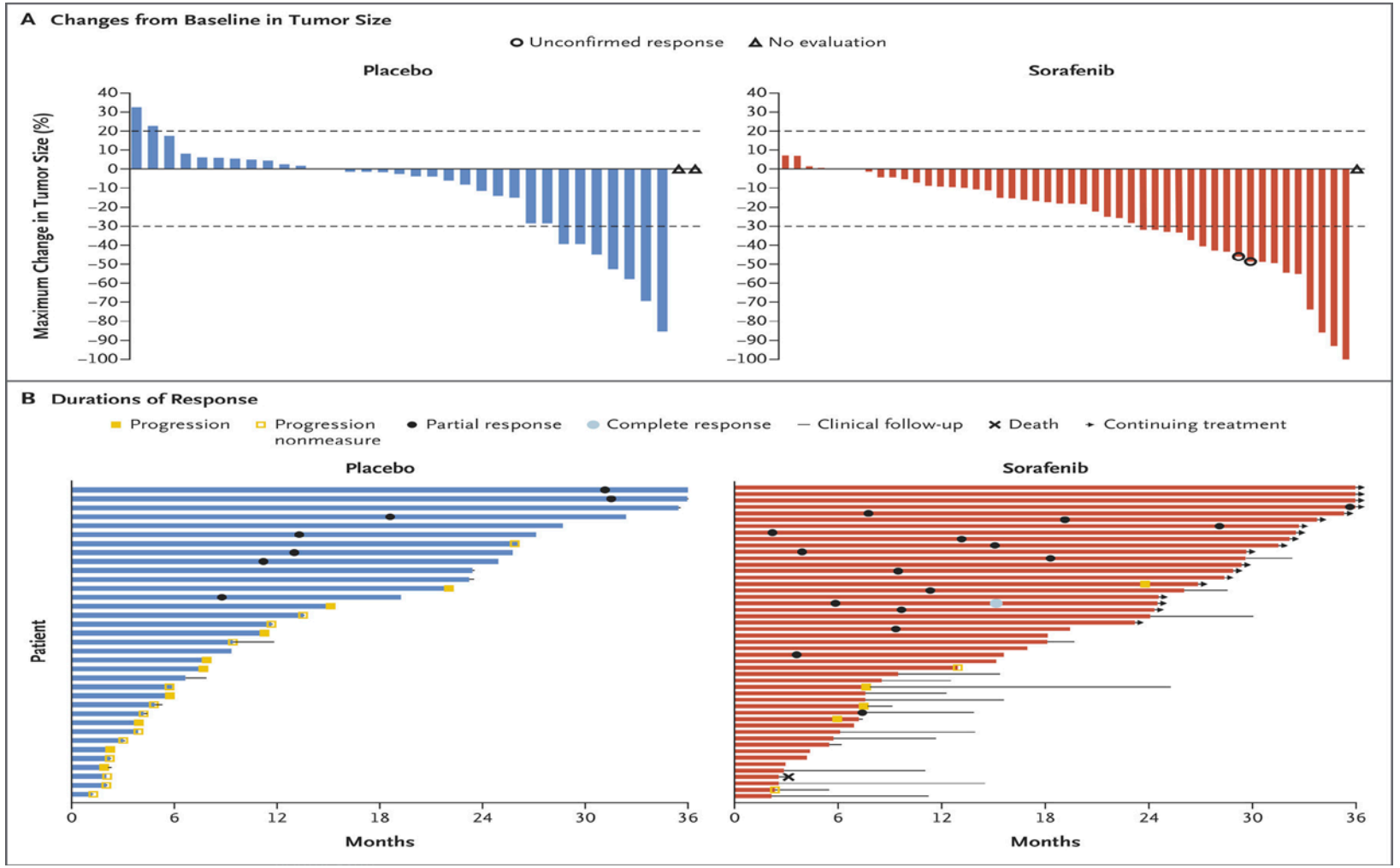
DESMOID FIBROMATOSIS

- Fibroblastic neoplasm – no metastatic potential
- Risk factors
  - Gardner syndrome – desmoid tumors in setting of FAP
    - Desmoids tend to be intra-abdominal, infiltrative
  - Pregnancy? – desmoids associated with high estrogen state
    - Abdomen or abd wall, Generally good outcomes, mostly anecdotal data
- Beta-catenin/Wnt signaling pathway activation
- Variable behavior; often indolent, some spontaneous regression

DESMOID TUMORS – TREATMENT

- Observation
- Surgery
  - Up to 40% recur w/neg margins
- Radiation therapy
- Tamoxifen, NSAID - 50%+ CBR ?
- Sorafenib – only randomized data currently available (**see next slide**)
- Other TKI – e.g. pazopanib
- Doxorubicin, MTX/vinorelbine
- Gamma secretase inhibitor – **ongoing studies, Nirogacestat phase 3 awaiting results**
- Cryoablation mRECIST response rate 72% (Tremblay, J Surg Oncol 2019;120:366)

Placebo vs. Sorafenib, Allliance 091105



Objective RR (RECIST v1.1)

- **Sorafenib – 33% (CI 20-48)**
- **Placebo – 20% (CI 8-37)**

MM Gounder et al. N Engl J Med 2018;379:2417-2428.

Nirogacestat – gamma secretase inhibitor

- Data presented ESMO, September 2022
- 142 patients with progressive/symptomatic desmoid tumors
- Randomized to nirogacestat or placebo
- Response rate – 41% vs 7%
- Median PFS – not reached in nirogacestat arm, vs 15.1 mos
- Statistically significant improvements in pain, role functioning, overall QOL
- 95% of all treatment-emergent AE's grade 1 or 2
- Nausea, diarrhea, fatigue, ovarian dysfunction

Summary

- Neoadjuvant anthracycline/ifosfamide in *selected* STS patients
  - Increasing data to support
  - Patient selection tools, tailored treatment options – still work to do
- Metastatic soft tissue sarcoma
  - Slow increase in treatment options – need more drugs, trials
  - Immunotherapy - exciting advances
- GIST
  - Mutation profiling is important
  - Ongoing development of new treatment options
- Desmoid tumors
  - Observation sometimes appropriate
  - Sorafenib is a reasonable first line systemic therapy, when indicated
  - Keep eyes open for Nirogacestat approval

MCW Sarcoma Clinical Trials

- Tcell Receptor trial – Synovial sarcoma
- PD1 +/- CTLA4 inhibitor – undifferentiated and myxofibrosarcoma
- Taxol +/- Nivolumab – angiosarcoma
- Abemaciclib – sarcoma or chordoma w/CDK pathway mutation
- Oral CDK9 inhibitor – Ewing sarcoma

- Other upcoming trials

- Contact me if any questions:
  - –Cell 414-331-2740
  - –jcharlso@mcw.edu