

Sarcoma: subtype tests, treatment by setting, drugs by subtype and side effects

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A. Subtype tests and what they change

Translocation-driven

- Synovial: SS18::SSX
- Myxoid liposarcoma: FUS::DDIT3
- Ewing: EWSR1::FLI1 (~85%)
- Alveolar RMS: PAX3/7::FOXO1
- DSRCT: EWSR1::WT1
- Younger patients; simple karyotype

Amplification

- WD / dedifferentiated liposarcoma
- MDM2 and CDK4 (12q13–15)
- MDM2 FISH separates them from lipoma
- Palbociclib, MDM2 inhibitors in trials

Complex karyotype

- UPS, myxofibrosarcoma
- Leiomyosarcoma
- Osteosarcoma, MPNST, angiosarcoma
- Older adults; TP53/RB1 loss
- Chemotherapy-responsive to a degree

Single driver / pathway

- GIST: KIT/PDGFRA
- Desmoid: CTNNB1/APC
- PEComa: TSC1/2 → mTOR
- Any: NTRK fusion (rare, test)
- Matched drugs work best

Why it matters: the subtype, not the word "sarcoma", decides chemosensitivity, the drug and the follow-up scans.

Four families by genetics. Translocation sarcomas affect younger people and carry diagnostic fusions; amplified MDM2/CDK4 marks well-differentiated and dedifferentiated liposarcoma; complex-karyotype sarcomas dominate in older adults; a few have one targetable driver.

Table A. Subtype tests and what they change

Subtype	Key IHC	Molecular test	What it changes
Well-differentiated / dedifferentiated liposarcoma	MDM2, CDK4 (nuclear)	MDM2 amplification (FISH)	Separates atypical lipomatous tumour from lipoma; DD liposarcoma: CDK4/6 inhibitor option later; retroperitoneal follow-up for life
Myxoid liposarcoma	DDIT3 (some labs)	FUS::DDIT3 or EWSR1::DDIT3	Very radiosensitive (36 Gy studied in DOREMY); spine MRI and CT abdomen for extrapulmonary spread; trabectedin works
Synovial sarcoma	TLE1, SS18–SSX fusion-specific antibody	SS18::SSX1/2/4	Chemosensitive (ifosfamide); afami-cel if HLA-A*02 and MAGE-A4 positive; may arise anywhere, at any age
Leiomyosarcoma	Desmin, SMA, h-caldesmon	Complex karyotype (no single test)	Doxorubicin + trabectedin first line if fit; scan liver as well as lung

Subtype	Key IHC	Molecular test	What it changes
Undifferentiated pleomorphic sarcoma	Diagnosis of exclusion (panel negative)	Exclude dedifferentiated liposarcoma (MDM2), melanoma, carcinoma	Most immunotherapy-responsive common STS; neoadjuvant pembrolizumab + RT option in stage III limb UPS
Angiosarcoma	CD31, ERG, CD34	<i>MYC</i> amplification (radiation-associated)	<i>MYC</i> helps separate post-RT angiosarcoma from atypical vascular lesion; taxane first; immunotherapy for scalp/face
MPNST	Loss of H3K27me3; S100/SOX10 patchy	NF1 (germline in half)	Genetics referral; poorly chemosensitive; pazopanib later
Ewing sarcoma	CD99 (membranous), NKX2.2	<i>EWSR1::FLI1</i> (~85%) or <i>::ERG</i> ; FISH or RT-PCR/NGS	Paediatric-type chemotherapy at any age; CIC- and BCOR-rearranged sarcomas are now separate entities
Rhabdomyosarcoma	Desmin, myogenin, MyoD1	<i>PAX3/7::FOXO1</i> (alveolar)	Fusion-positive = higher risk; multimodality protocol with chemotherapy
Osteosarcoma	SATB2 (osteoid matrix on H&E)	Complex karyotype; MDM2 in low-grade central and parosteal types	Low-grade parosteal: surgery alone; conventional high-grade: MAP chemotherapy
Chondrosarcoma	S100	<i>IDH1/2</i> mutation (most conventional)	Surgery; IDH inhibitors in trials; dedifferentiated: osteosarcoma-style chemotherapy
PEComa	HMB45, melan-A + SMA/desmin	<i>TSC1/2</i> loss; <i>TFE3</i> fusion subset	mTOR inhibitor (nab-sirolimus) for advanced disease
Any advanced sarcoma, especially infantile fibrosarcoma, young adults	pan-TRK	<i>NTRK1–3</i> fusions (RNA NGS)	Larotrectinib or entrectinib: high and durable response rates
GIST and desmoid (separate diseases)	KIT/DOG1; nuclear β -catenin	<i>KIT/PDGFRA</i> ; <i>CTNNB1/APC</i>	Not treated like sarcoma: imatinib for GIST; observation first for desmoid

B. Treatment by setting

Feature	Preoperative RT (preferred)	Postoperative RT
Dose	50 Gy in 25 fractions	60–66 Gy (higher if margin positive)
Volume	Smaller: tumour seen on MRI	Larger: operative bed, scar, drains
Wound complications	More: ~35% (mostly lower limb)	Fewer: ~17%
Late fibrosis, oedema, stiffness	Less: grade ≥2 fibrosis ~32%	More: ~48%, permanent
Surgery	4–6 weeks after RT	RT starts 4–6 weeks after surgery
Best for	Most grade 2–3 or large tumours	Infiltrative myxofibrosarcoma; wound risk

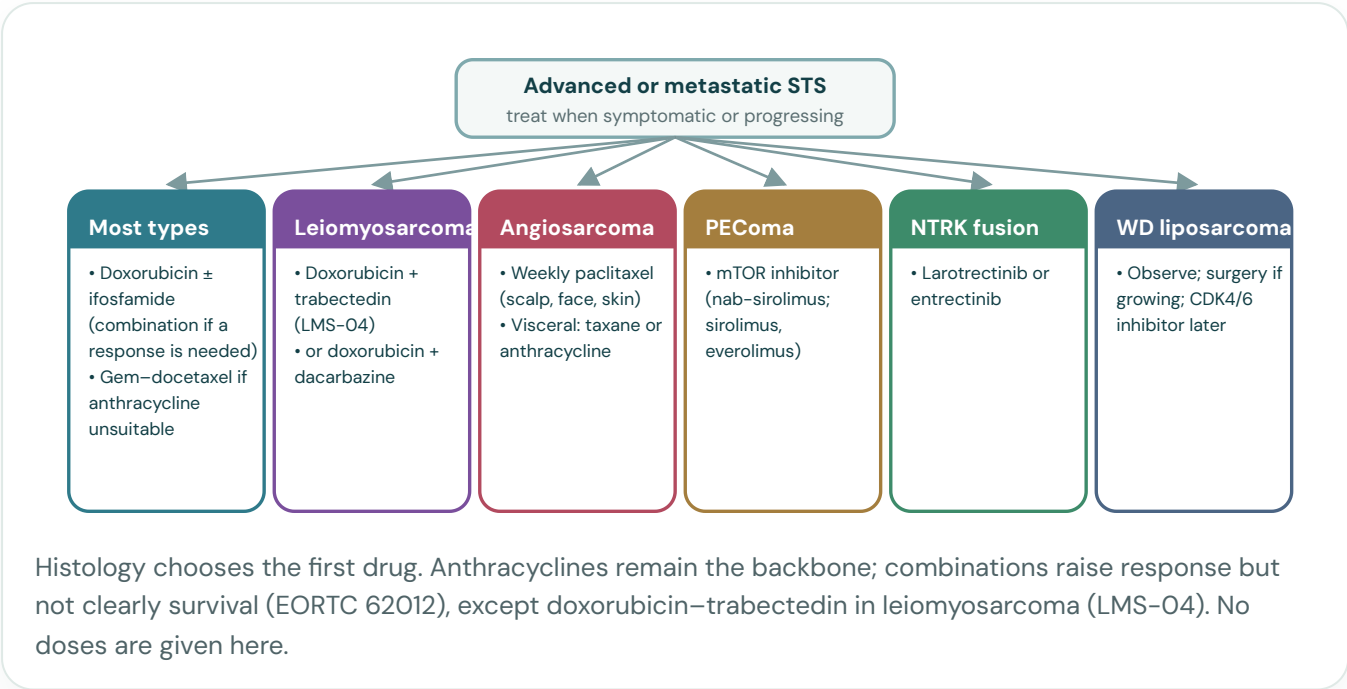
Timing trades early wound problems for late limb function. In the NCIC SR2 trial local control and survival were the same; preoperative RT caused more wound complications, postoperative RT more permanent fibrosis, oedema and joint stiffness. IMRT reduces both.

Table B. Treatment by setting (no doses)

Setting	Standard	Alternatives / notes	Evidence
Limb/trunk STS, superficial, ≤5 cm, low grade	Wide excision alone	Re-excise if margin positive	NCI 1998
Limb/trunk STS, >5 cm or deep, grade 2–3	Preoperative RT 50 Gy/25 → wide excision 4–6 weeks later	Postoperative RT (60–66 Gy) if surgery first; IMRT preferred	NCIC SR2, Folkert 2014
Stage III limb UPS (or DD/pleomorphic liposarcoma)	Preoperative RT + pembrolizumab → surgery → adjuvant pembrolizumab (shared decision)	Survival data immature; not tested with chemotherapy	SU2C–SARC032
High-risk limb/trunk STS (large, deep, grade 3, chemosensitive type)	Consider 3 cycles of anthracycline + ifosfamide (neoadjuvant or adjuvant), fit patients	Benefit modest and uncertain; synovial and myxoid LPS most responsive	ISG–STS 1001, Pervaiz 2008, EORTC 62931
Myxoid liposarcoma, preoperative	RT 50 Gy (36 Gy de-escalation in trials)	Very radiosensitive	DOREMY
Retroperitoneal sarcoma, resectable	Complete en bloc resection in a reference centre	Preoperative RT only for selected WD / low-grade DD liposarcoma; no routine adjuvant therapy	STRASS, TARPSWG 2021
Unplanned excision ("whoops")	MRI then re-excision of the scar and bed (± RT)	Residual tumour found in about half	Noria 1996

Setting	Standard	Alternatives / notes	Evidence
Oligometastatic lung disease	Metastasectomy (VATS) if all disease removable and interval long	SBRT or ablation if unfit	Chudgar 2017, Dhakal 2012
Metastatic STS, first line	Doxorubicin (single agent if palliation is the goal; + ifosfamide if a response is needed)	LMS: doxorubicin + trabectedin; angiosarcoma: paclitaxel; PEComa: mTOR; NTRK: TRK inhibitor	EORTC 62012, LMS-04, ANGIOTAX
Osteosarcoma, localised (high grade)	Age <40: MAP 10 weeks → wide resection → MAP to 29 weeks; ≥40: doxorubicin–cisplatin	Poor necrosis: no change of regimen; no adjuvant RT after complete resection	MIOS, EURAMOS-1
Ewing sarcoma, localised	VDC/IE every 14 days (<18; 14 or 21 days ≥18) × 12 weeks → surgery or RT → 14–17 cycles in total	RT with chemotherapy (no doxorubicin during RT); adults: same protocol at full intensity	INT-0091, AEWS0031, Euro Ewing 2012
Conventional chondrosarcoma	Surgery (curettage for grade 1 limb; wide resection otherwise)	RT for unresectable skull base/axial (high dose, often protons)	ESMO–EURACAN–GENTURIS

C. Drugs by subtype in advanced soft tissue sarcoma



Leiomyosarcoma	Gem–docetaxel → trabectedin, pazopanib, eribulin, dacarbazine
Liposarcoma (DD, pleomorphic)	Gem–docetaxel → eribulin (OS gain); CDK4/6 inhibitor if indolent; no pazopanib
Myxoid / round cell liposarcoma	Trabectedin (targets FUS::DDIT3); eribulin; afami–cel if HLA/MAGE–A4 fit
Synovial sarcoma	Ifosfamide → pazopanib, trabectedin; afami–cel (HLA–A*O2, MAGE–A4)
UPS, myxofibrosarcoma	Gem–docetaxel → pazopanib; pembrolizumab or nivolumab–ipilimumab
Angiosarcoma	Taxane ↔ anthracycline; then gemcitabine, pazopanib, checkpoint inhibitors (scalp/face)
MPNST	Ifosfamide/anthracycline → pazopanib; trials
Alveolar soft part, clear cell	Checkpoint inhibitors (atezolizumab in ASPS); chemotherapy rarely works

After the first line, the subtype map matters even more. Trial enrolment is preferred at every step; pazopanib is not used for adipocytic sarcomas, and responses to later lines are modest, so quality of life leads the decision.

Table C. Drugs by subtype in advanced soft tissue sarcoma (no doses)

Subtype	First line	Later lines	Avoid / note
Most anthracycline–sensitive types (UPS, synovial, pleomorphic LPS, myxofibrosarcoma)	Doxorubicin ± ifosfamide	Gemcitabine–docetaxel; pazopanib; trabectedin; immunotherapy (UPS)	Combination only when a response is needed (more toxicity, no clear OS gain)
Leiomyosarcoma (uterine and non–uterine)	Doxorubicin + trabectedin, or doxorubicin + dacarbazine	Gemcitabine–docetaxel, trabectedin, pazopanib, eribulin	Check liver as well as lung on scans
Liposarcoma, dedifferentiated/pleomorphic	Doxorubicin	Gemcitabine–docetaxel → eribulin; CDK4/6 inhibitor if indolent	No pazopanib in adipocytic sarcoma
Liposarcoma, myxoid/round cell	Doxorubicin (± ifosfamide)	Trabectedin; eribulin; afami–cel if eligible	Image spine and abdomen
Synovial sarcoma	Doxorubicin ± ifosfamide	Ifosfamide; pazopanib; trabectedin; afami–cel	HLA–A*O2 typing and MAGE–A4 IHC to check cell–therapy eligibility
Angiosarcoma	Weekly paclitaxel (cutaneous/scalp); taxane or doxorubicin (visceral)	Switch class; gemcitabine; pazopanib; checkpoint inhibitors	Radiation–associated breast angiosarcoma: surgery is the main treatment when localised
MPNST	Doxorubicin + ifosfamide	Pazopanib	NF1 genetics; low response rates

Subtype	First line	Later lines	Avoid / note
PEComa	nab-sirolimus (or sirolimus/everolimus)	Chemotherapy has little activity	Hyperglycaemia, stomatitis, pneumonitis
NTRK fusion-positive (any)	Larotrectinib or entrectinib	Repotrectinib for resistance	Test with RNA NGS where possible
Alveolar soft part sarcoma	Observe if limited and stable; atezolizumab or pembrolizumab if progressing; + axitinib if bulky	Pazopanib, sunitinib	Chemotherapy ineffective; brain MRI

D. Managing common side effects

Table D. Managing common side effects of sarcoma drugs

Drug	Main problems	Check / prevent	Act on
Doxorubicin	Cardiomyopathy (cumulative), mucositis, alopecia, myelosuppression, extravasation injury	Echo or MUGA before; track lifetime dose; central line if vesicant risk	Breathlessness, oedema, falling ejection fraction: stop; cardiology
Ifosfamide	Encephalopathy, haemorrhagic cystitis, proximal tubulopathy (Fanconi), myelosuppression	Mesna, hydration, urine for blood; renal function, phosphate, bicarbonate	Confusion or drowsiness: stop infusion; methylene blue per protocol
Trabectedin	Transaminitis, neutropenia, rhabdomyolysis, fatigue	Central line; dexamethasone premedication; LFTs and CK each cycle	Rising CK or bilirubin: delay or reduce
Gemcitabine–docetaxel	Myelosuppression, fluid retention, pneumonitis, nail changes	Growth–factor support; steroid premedication for docetaxel	New cough or breathlessness: exclude pneumonitis
Pazopanib	Hepatotoxicity, hypertension, diarrhoea, hair depigmentation, pneumothorax with lung metastases	LFTs at 3, 5, 7, 9 weeks then monthly; BP; caution with many lung metastases	ALT >3× ULN: interrupt
Eribulin, paclitaxel	Neuropathy, neutropenia	Ask about numbness every cycle	Grade 2 neuropathy: delay/reduce
Pembrolizumab, nivolumab–ipilimumab	Immune–related colitis, hepatitis, pneumonitis, endocrine	TSH, cortisol, LFTs; patient alert card	Steroids by grade; hold drug
Afamitresgene autoleucel	Cytokine release syndrome, cytopenias, (rarely) neurotoxicity	Lymphodepletion in a cell–therapy centre	Fever after infusion: CRS protocol (tocilizumab)
High–dose methotrexate (osteosarcoma)	Acute kidney injury, mucositis, hepatitis	Hydration, urine alkalinisation, levels, leucovorin rescue; avoid NSAIDs, PPIs, co–trimoxazole	Delayed clearance: glucarpidase
Cisplatin (osteosarcoma)	Ototoxicity, nephrotoxicity, emesis	Audiometry; magnesium	Hearing loss: discuss modification
Cyclophosphamide, ifosfamide, etoposide (Ewing)	Infertility, second leukaemia, cystitis	Sperm banking or ovarian protection before treatment	Long–term survivorship clinic