

ONCOLOGY UPDATES

# Bone & Soft Tissue Cancers

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Three frontiers reshaping systemic therapy — engineered cell therapy, checkpoint immunotherapy, and targeting the CDK4 in liposarcoma.

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# Why now? A field long overdue for momentum



Soft-tissue and bone sarcomas are **>100 heterogeneous mesenchymal cancers** making up ~1% of adult cancers. For most of the past decade, systemic options were few and benefits were modest.

**That is changing:** a wave of first-in-class approvals and the first-ever positive phase 3 trials are now redefining the standard of care across distinct subtypes.

**>100**

histologic subtypes

**~1%**

of adult cancers

**01**



## TCR Cell Therapy

Engineered T-cell receptor therapy enters solid tumors

**02**



## PD-1 in Subsets

Histology-selective benefit from checkpoint blockade

**03**



## CDK4 / MDM2 Axis

First positive phase 3 in dedifferentiated liposarcoma

01



## TCR Cell Therapy

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*The first engineered T-cell receptor therapy approved for a solid tumor.*

# Afami-cel (Tecelra): how it works & where it stands



## Mechanism

**Autologous T cells engineered with an enhanced-affinity TCR** targeting MAGE-A4, a cancer-testis antigen restricted to germ cells and re-expressed in synovial sarcoma.

**HLA-A\*02–restricted recognition** of the MAGE-A4 peptide on the tumor cell surface.

**Delivery:** fludarabine/cyclophosphamide lymphodepletion, then a single one-time infusion.



## Regulatory status

**Aug 2024** — accelerated approval; first engineered TCR-T therapy ever approved for a solid tumor.

**2026** — converted to full approval and expanded to patients  $\geq 12$  years of age.

### Eligibility requires:

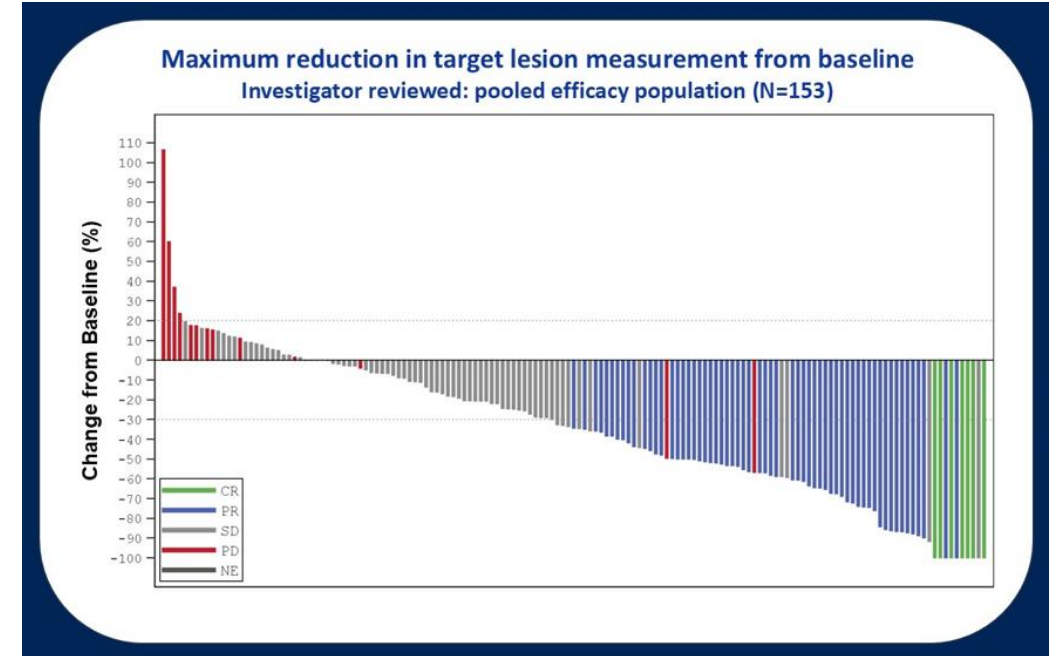
- HLA-A\*02:01/02/03/06 positivity
- MAGE-A4 expression by companion diagnostic
- prior chemotherapy

# Afami-cel: pooled efficacy & safety

*SPEARHEAD-1 + SyS pilot · n = 153 · median follow-up 46 months*

**43.8%**

Objective response



## Depth & durability

### 7 complete responses (4.6%)

in a heavily pre-treated population (median 3 prior lines).

**~25% of responders maintained response ≥24 months**

— a durable benefit rare in metastatic synovial sarcoma.



## Safety signature

**Cytokine release syndrome 73%** — mostly low grade (grade ≥3 ~3%).

**ICANS uncommon** and largely grade 1–2.

**Prolonged cytopenias** are the main lingering toxicity; corticosteroids avoided to preserve T-cell activity.

# Afami-cel: pooled efficacy & safety

SPEARHEAD-1 + SyS pilot · n = 153 · median follow-up 46 months

20.2 mo

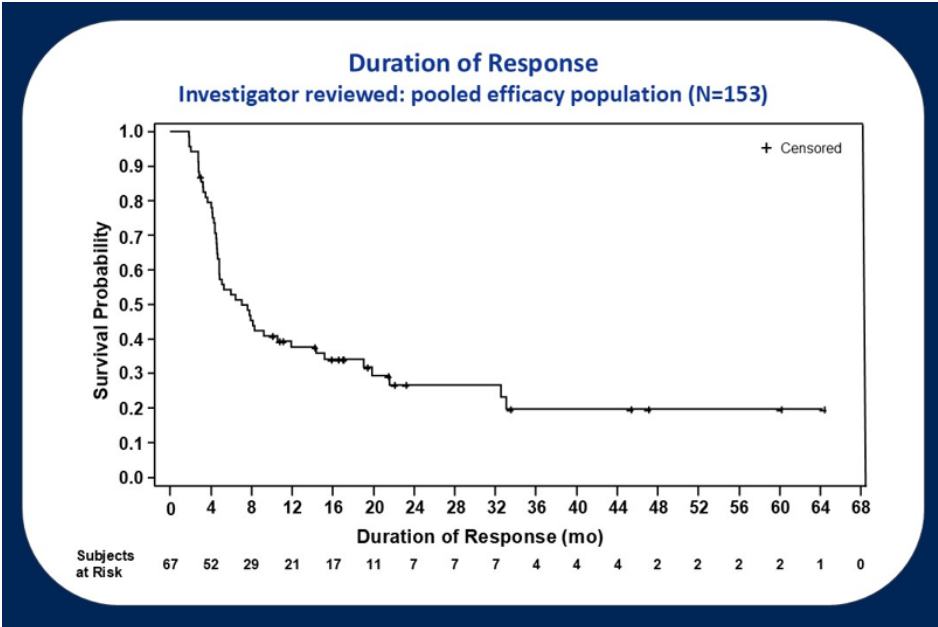
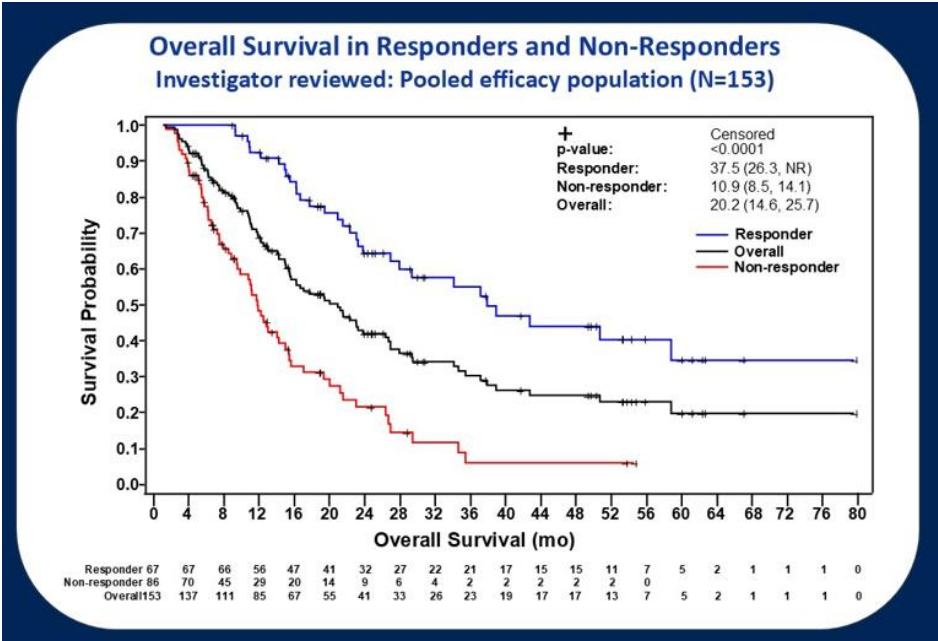
Median overall survival

7.1 mo

Median duration of response

4.0 mo

Median PFS



# Beyond afami-cel: pipeline & practical realities



## Broadening the pipeline

**Lete-cel** — the next late-stage TCR-T, targeting **NY-ESO-1** rather than MAGE-A4.

Extends the engineered-TCR approach to **synovial sarcoma and myxoid / round cell liposarcoma**, widening both the antigen base and the eligible histologies.

*Signals a maturing class — not a one-product story.*



## The practical funnel

- › **Eligibility screen** HLA typing + antigen testing exclude a large share of patients before treatment is possible.
- › **Manufacturing** Leukapheresis, engineering and release create a vein-to-vein interval — disease can progress meanwhile.
- › **Delivery setting** Lymphodepletion and CRS/ICANS monitoring require specialized, certified centers.
- › **Access & cost** A high-cost one-time therapy raises real equity and logistics questions.

# 02



## PD-1 Inhibitors in Sarcoma Subsets

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*From “cold” tumors to histology-selective benefit.*



# Not all sarcomas are equal: who actually benefits

Pooled across 9 ICI trials (384 patients):

**15.1%**

overall response rate

**9.8%**

*once alveolar soft-part sarcoma is excluded — the benefit is concentrated, not broad.*

## Histologies enriched for response

### Alveolar soft-part sarcoma

Atezolizumab FDA-approved (2022); the standout responder.

### Angiosarcoma

Particularly cutaneous head & neck disease.

### Undifferentiated pleomorphic sarcoma

Higher mutational/inflammatory profile.

### Dedifferentiated liposarcoma

Selected responders; rationale for combinations.

### Clear cell sarcoma

Emerging signal in a historically hard subtype.

### Biomarker note

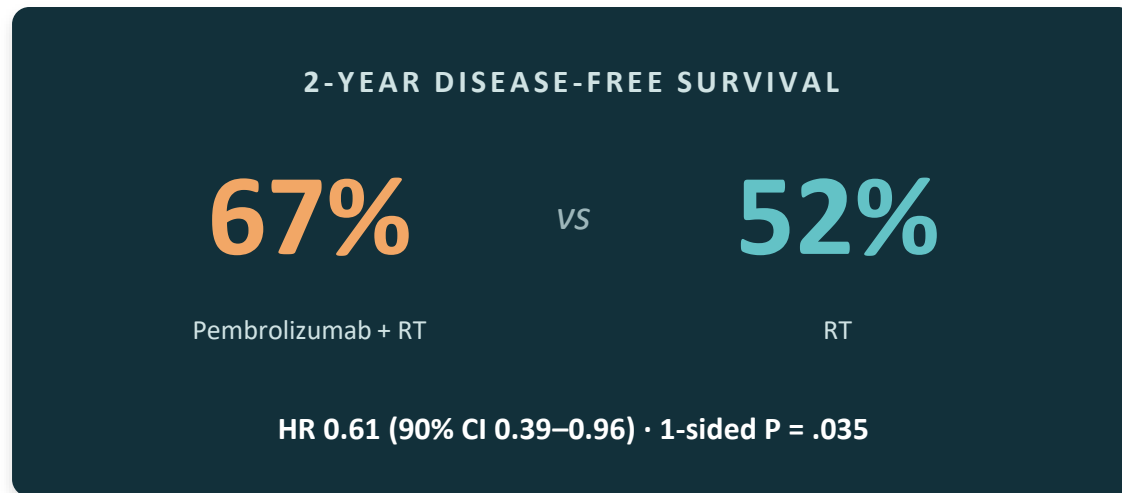
Enrich by histology — TMB has limited utility in STS.

# SARC032: immunotherapy moves into curable disease

SU2C-SARC032 · phase 2 randomized · stage III UPS / liposarcoma of the extremity · n = 143 · The Lancet 2025



Control arm: radiotherapy + surgery alone (no pembrolizumab)



## Why it matters

**First randomized trial** to add checkpoint blockade to radiotherapy + surgery in high-risk localized STS.

**Benefit concentrated in grade 3 disease** — no clear difference in the grade 2 subgroup (HR 0.84).

**Well tolerated**, with infrequent surgical complications.

# Raising the bar: combinations & biomarkers



## Chemo-immunotherapy, front line

**EA7222** (ECOG-ACRIN) — randomized phase 3 of **doxorubicin ± pembrolizumab** as first-line therapy.

**Population:** metastatic / unresectable UPS, DDLPS and related poorly differentiated sarcomas (anthracycline-naïve). Primary endpoint PFS; also tests upfront vs second-line pembrolizumab.

*Currently enrolling — built to turn frontline checkpoint use in UPS from anecdote into randomized evidence.*



## Predictive biomarkers

**Tertiary lymphoid structures (TLS)** — organized immune aggregates within the tumor — are emerging as the most promising predictor of checkpoint benefit in sarcoma.

**Tumor mutational burden** has limited discriminatory value here, given the generally cold, low-TMB microenvironment.

*The frontier: moving from histology-based selection toward TME-based selection.*

# 03



## Targeting the CDK4 in DDLPS

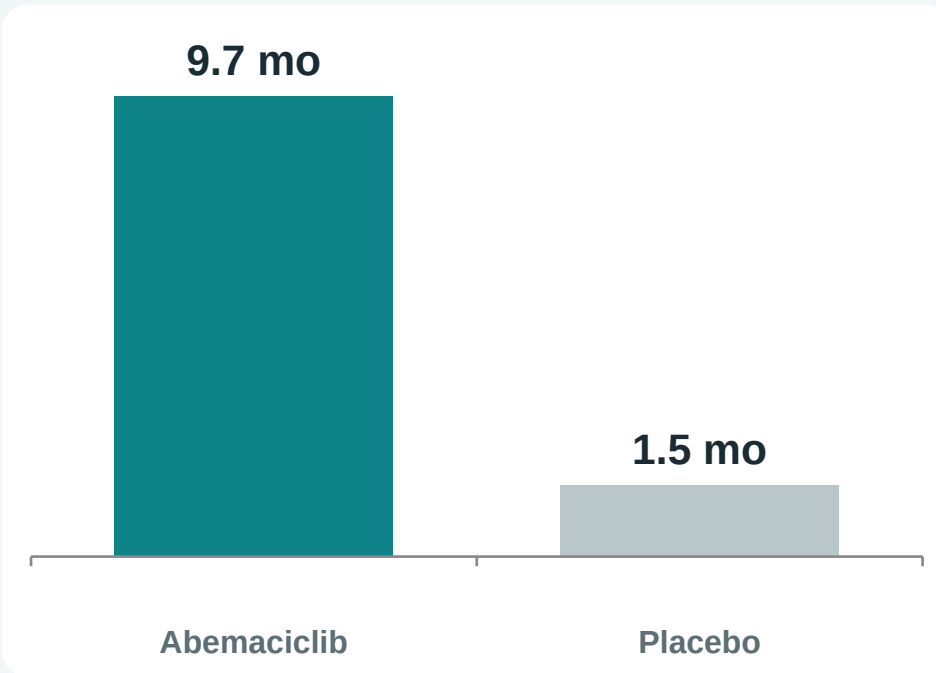
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*Near-universal 12q13–15 co-amplification — finally, druggable.*

# SARC041: the first positive phase 3 in DDLPS

*Abemaciclib vs placebo · recurrent / metastatic DDLPS · n = 108 · ASCO 2026 Plenary (LBA2)*

Median progression-free survival (months)



**HR 0.38** (90% CI 0.25–0.59,  $P < .001$ )

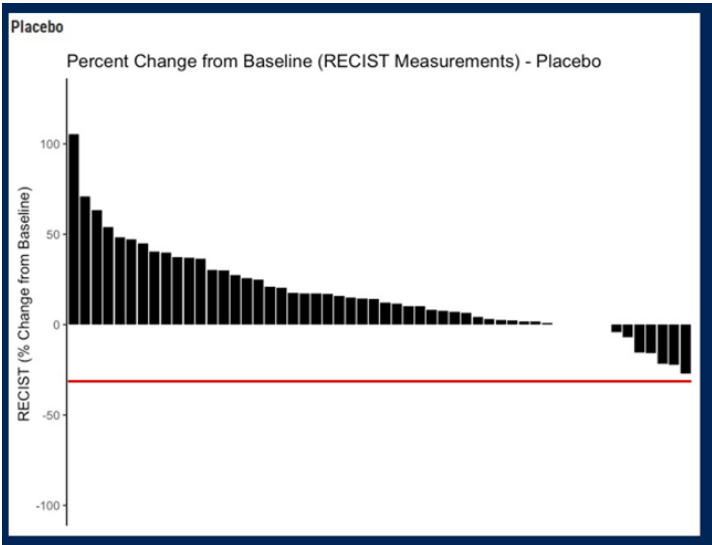
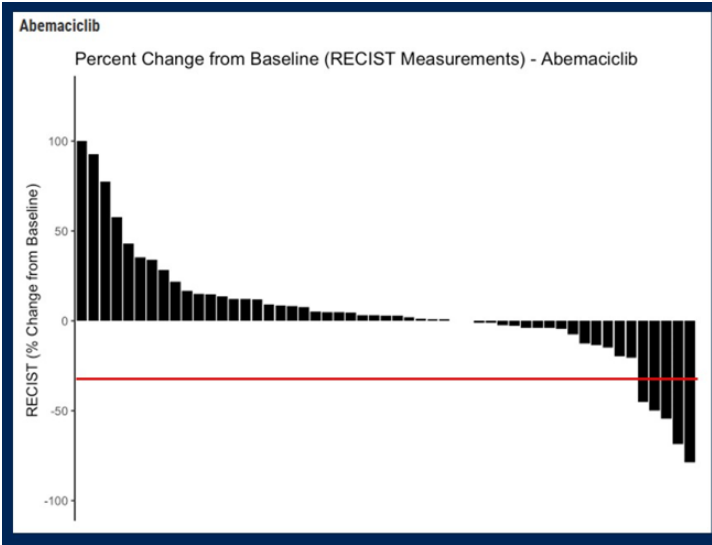
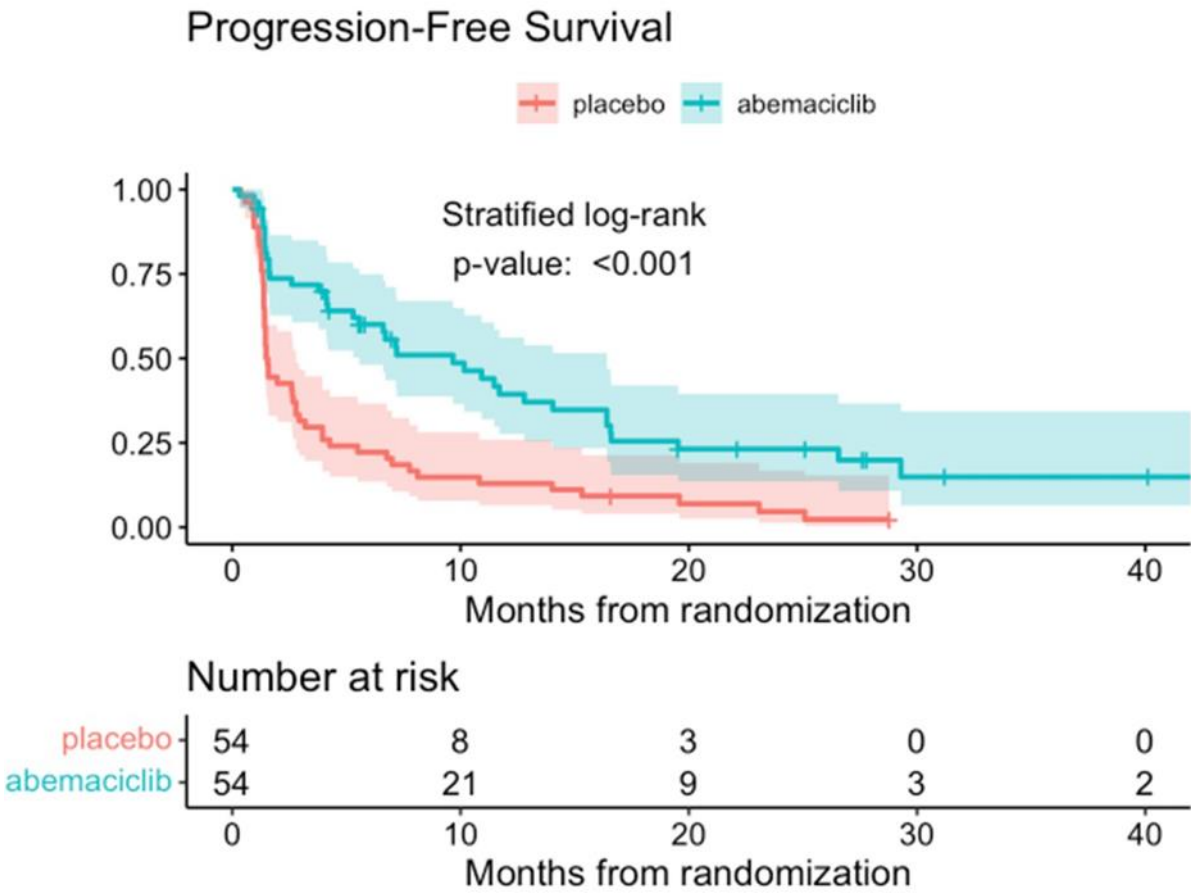
A 62% reduction in the risk of progression or death — PFS extended more than six-fold over placebo.

**Overall survival:** not reached vs 25.5 mo (HR 0.55,  $P = .07$ ) — a positive trend despite 85% of placebo patients crossing over.

**Read with care:** placebo comparator, not designed as a registration study — though abemaciclib is already on the NCCN compendium.

# SARC041: the first positive phase 3 in DDLPS

Abemaciclib vs placebo · recurrent / metastatic DDLPS · n = 108 · ASCO 2026 Plenary (LBA2)



# Key takeaways



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## TCR Cell Therapy

Afami-cel is the first engineered TCR-T approved for a solid tumor — durable responses in synovial sarcoma, now  $\geq 12$  years. Lete-cel broadens the class.

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**ORR 43.8% · OS 20.2 mo**



02

## PD-1 in Subsets

Benefit is histology-selective: striking in ASPS, meaningful in angiosarcoma/UPS/DDLPS. Dual checkpoint and TLS biomarkers are the next step.

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**Pooled ORR 15% → 10% w/o ASPS**



03

## CDK4 / MDM2 in DDLPS

SARC041 is the first positive phase 3 ever in DDLPS (abemaciclib).

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**PFS 9.7 vs 1.5 mo · HR 0.38**

# Implications & open questions



## What to watch as these move into practice

### Sequencing

Where do cell therapy and CDK4 inhibitor sit relative to anthracyclines and existing lines?

### Selection

Can we move from histology-based to TME- and biomarker-based patient selection (e.g. TLS)?

### Confirmation

SARC041's regulatory path remain to be settled.

### Earlier intervention

Does CDK4 inhibition help more if given earlier in the DDLPS disease course?

### Access & equity

High-cost, center-restricted cell therapy raises real delivery and equity questions.

### Wider momentum

Same era: nirogacestat (desmoid) and vimseltinib (TGCT, approved 2025) — the field is accelerating broadly.



# Thank you

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*Questions & discussion welcome*

## KEY REFERENCES

- D'Angelo SP, et al. Afami-cel (SPEARHEAD-1 + pilot pooled analysis), ASCO 2026.
- Dickson MA, et al. SARC041: abemaciclib vs placebo in DDLPS. ASCO 2026, LBA2 (Plenary).
- Mowery YM, et al. SU2C-SARC032: perioperative pembrolizumab + RT in localized high-risk STS. Lancet 2025.
- EA7222 (ECOG-ACRIN, NCT06422806): doxorubicin ± pembrolizumab in UPS/DDLPS, randomized phase 3 (enrolling).
- Italiano A, et al. PD1/PD-L1 in advanced STS: pooled analysis. J Hematol Oncol 2020;13:55 (ORR 15.1% → 9.8% excl. ASPS).
- NCCN Guidelines, Soft Tissue Sarcoma, v1.2025.