Adult soft tissue sarcoma: Updates from 2024-2025

Christopher Larson, M.D., Ph.D.
UCSD Moores Cancer Center
Sarcoma medical oncology

Disclosures
AdAPT-001 inventor
Scientist, EpicentRx

Overview

Perioperative

- Undifferentiated Pleomorphic Sarcoma
- Myxoid Liposarcoma

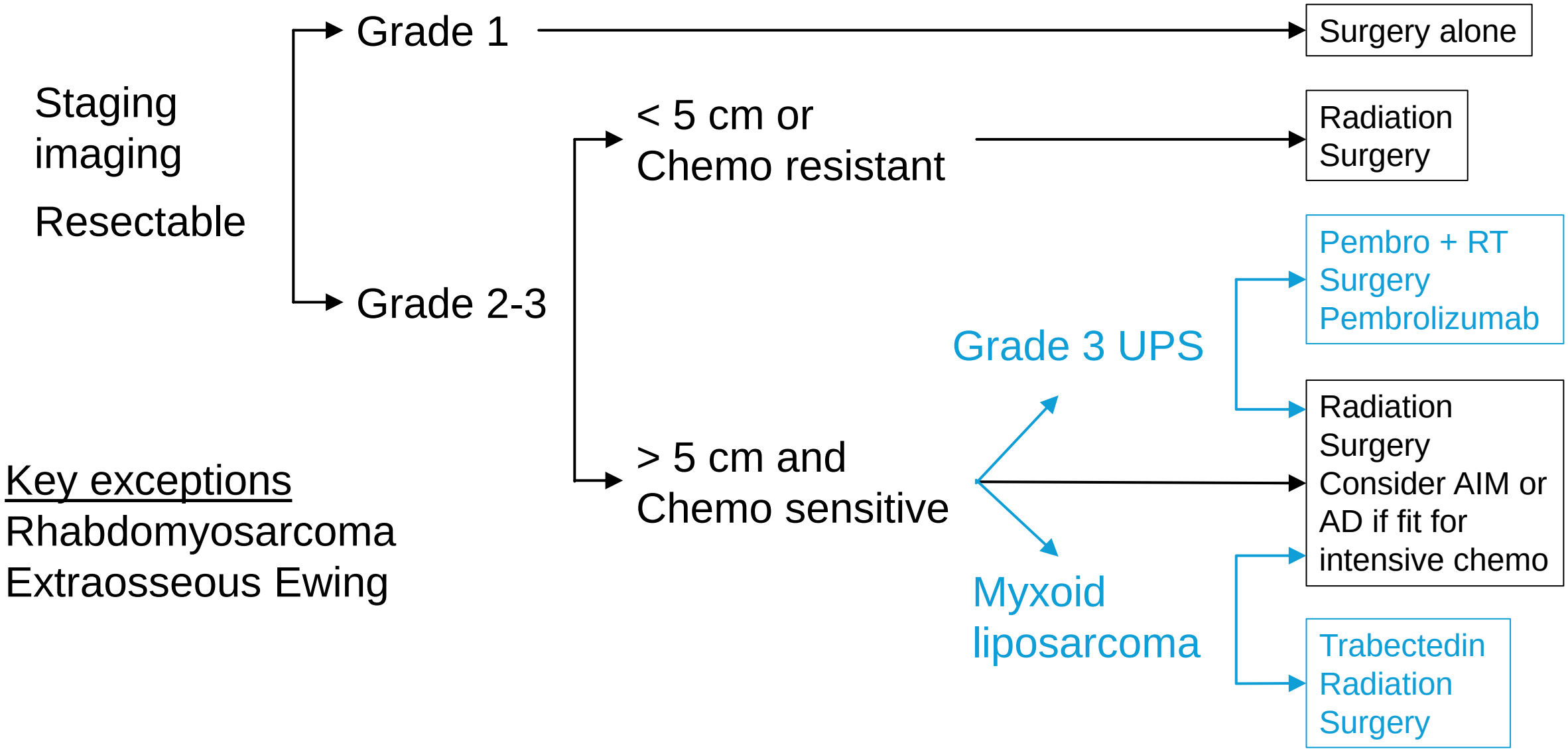
Unresectable

- Leiomyosarcoma
- Dedifferentiated Liposarcoma

Later line of therapy

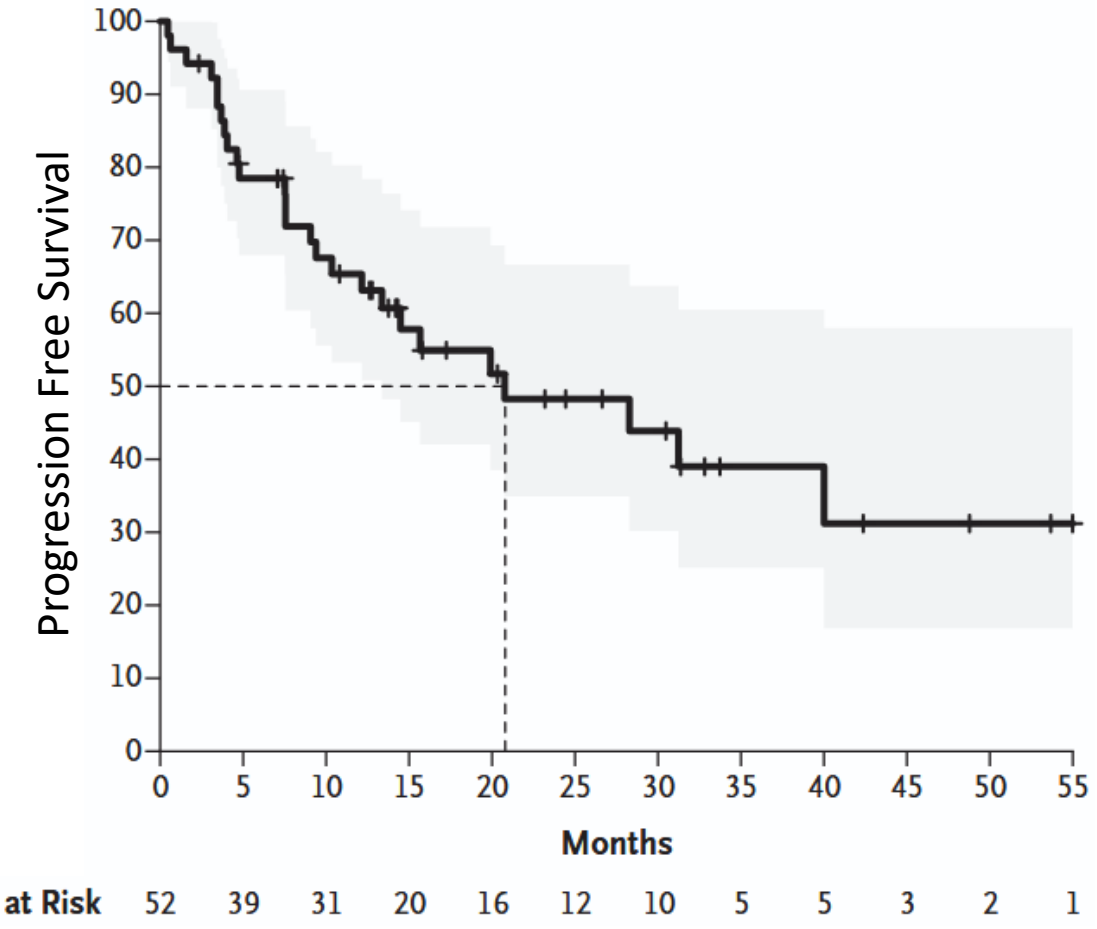
- Synovial Sarcoma

Resectable extremity soft tissue sarcoma: Early 2024 vs 2025



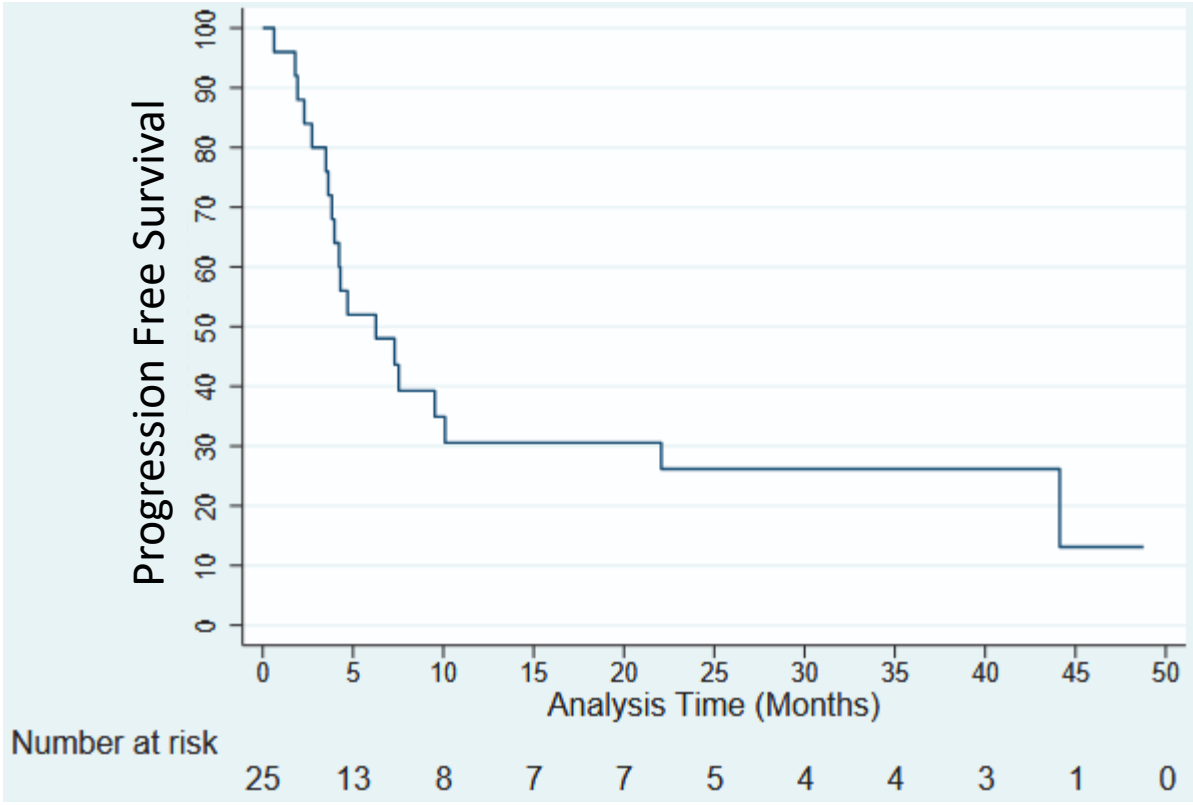
Checkpoint inhibitors in sarcoma subtypes

Alveolar soft part sarcoma – Atezolizumab



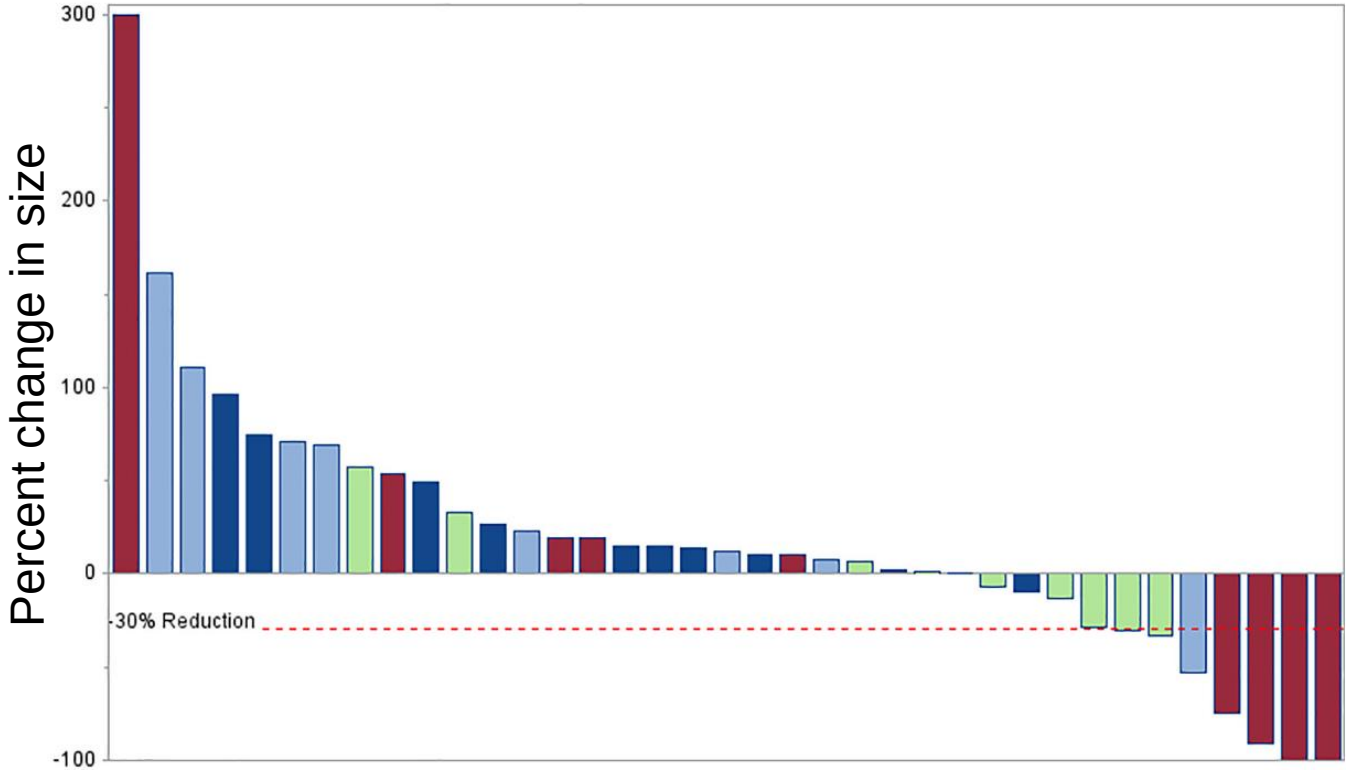
N Engl J Med 2023;389:911-21.

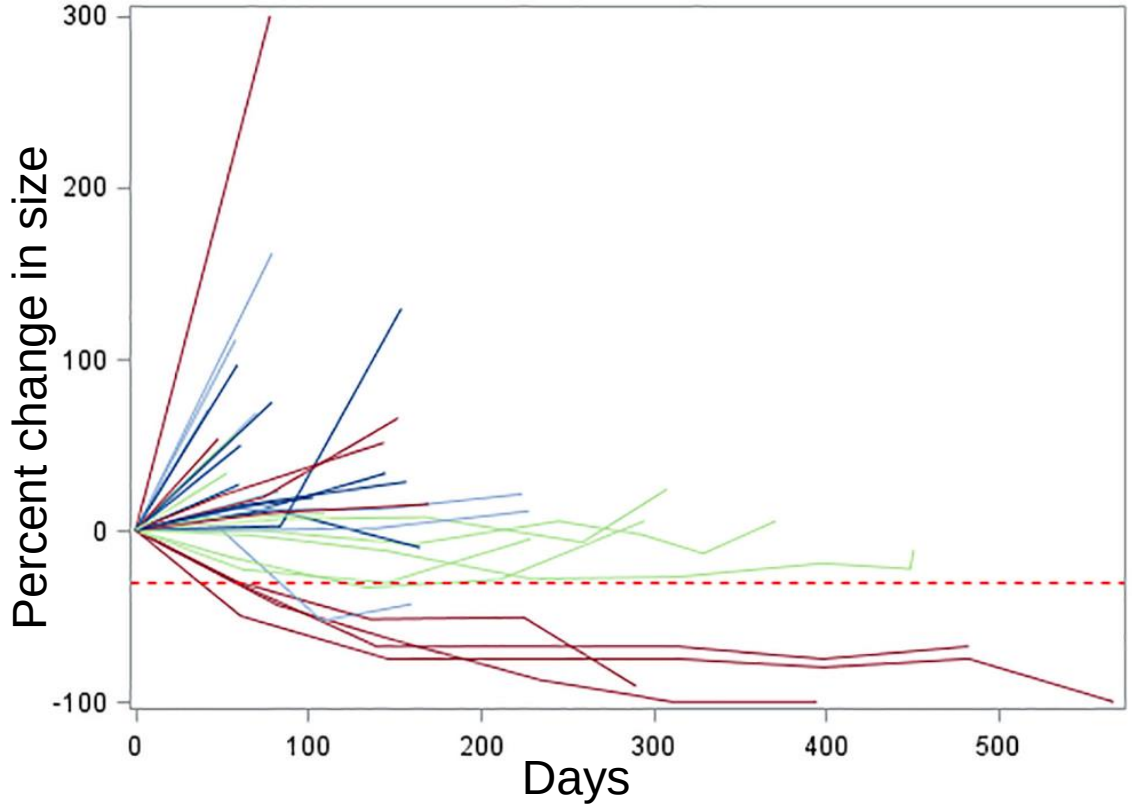
Angiosarcoma – Various CPIs, mostly pembro



Cancer 2022;128:3383-3391.

Checkpoint inhibitors in sarcoma subtypes
SARC 028 trial – Pembrolizumab





Expansion cohort response rates
UPS: 23% (9/40)
ddLPS: 10% (4/40)

Leiomyosarcoma
Pleomorphic undifferentiated sarcoma
Poorly differentiated/dedifferentiated Liposarcoma
Synovial sarcoma

Lancet Oncol. 2017 November ; 18(11): 1493–1501. ASCO 2019 abstract 11015

Safety and efficacy of pembrolizumab, radiation therapy, and surgery versus radiation therapy and surgery for stage III soft tissue sarcoma of the extremity (SU2C-SARC032): an open-label, randomised clinical trial

Resectable extremity UPS or dedifferentiated / pleomorphic LPS, >5 cm, grade 2-3

Control

Radiation (50 Gy in 25 fractions)
Resection

Experimental

Pembrolizumab (200 mg q3 weeks) ×3 doses
Radiation starting within 2 weeks of first dose
Resection
Pembrolizumab to complete 14 doses (~1 year total)

www.thelancet.com Published online November 12, 2024 https://doi.org/10.1016/S0140-6736(24)01812-9

Eligibile histologies

Dedifferentiated / pleomorphic liposarcoma

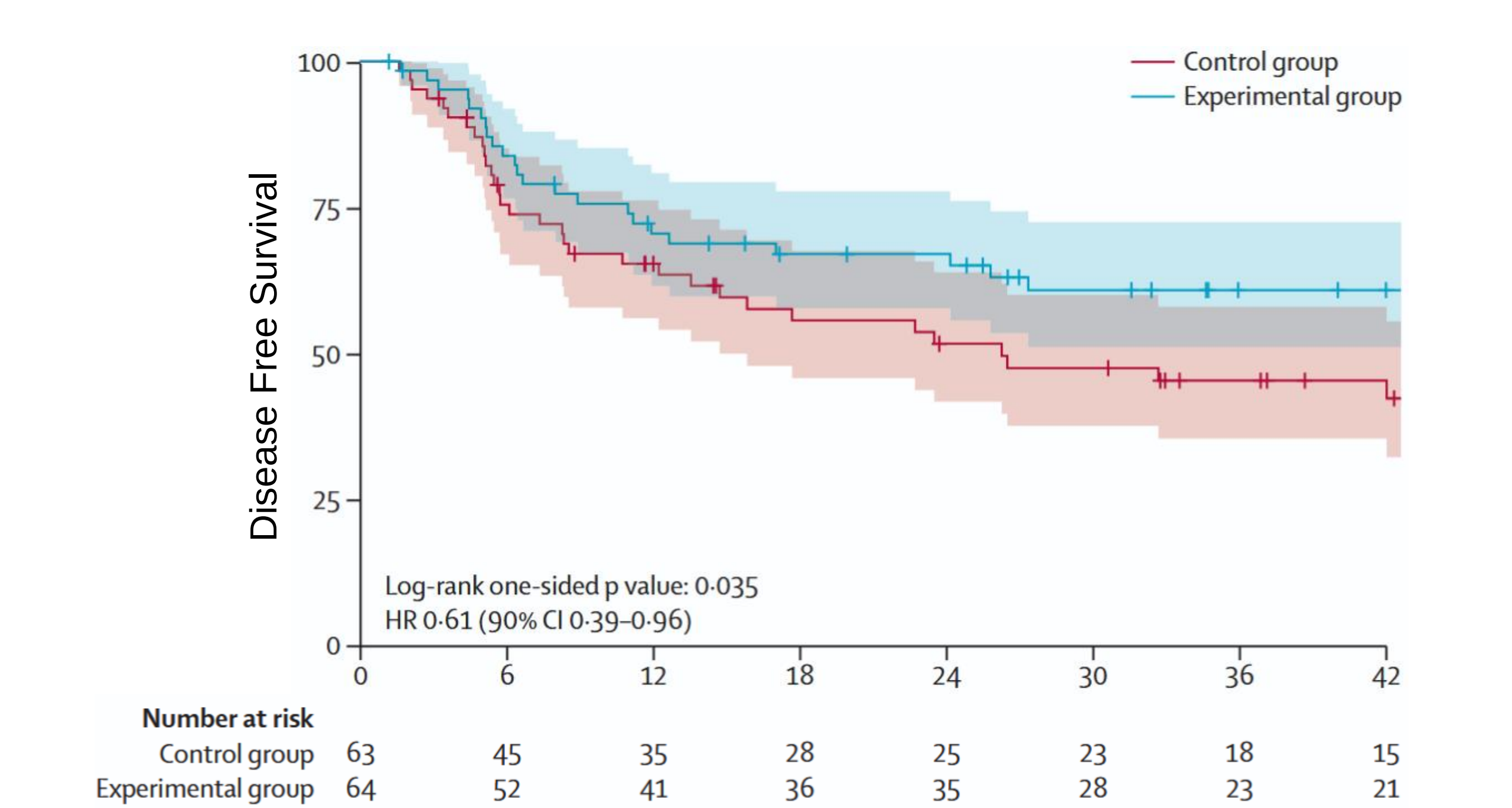
or

Undifferentiated Pleomorphic Sarcoma
Includes: Myxofibrosarcoma
Unclassified spindle cell sarcoma
Pleomorphic spindle cell sarcoma
Various others

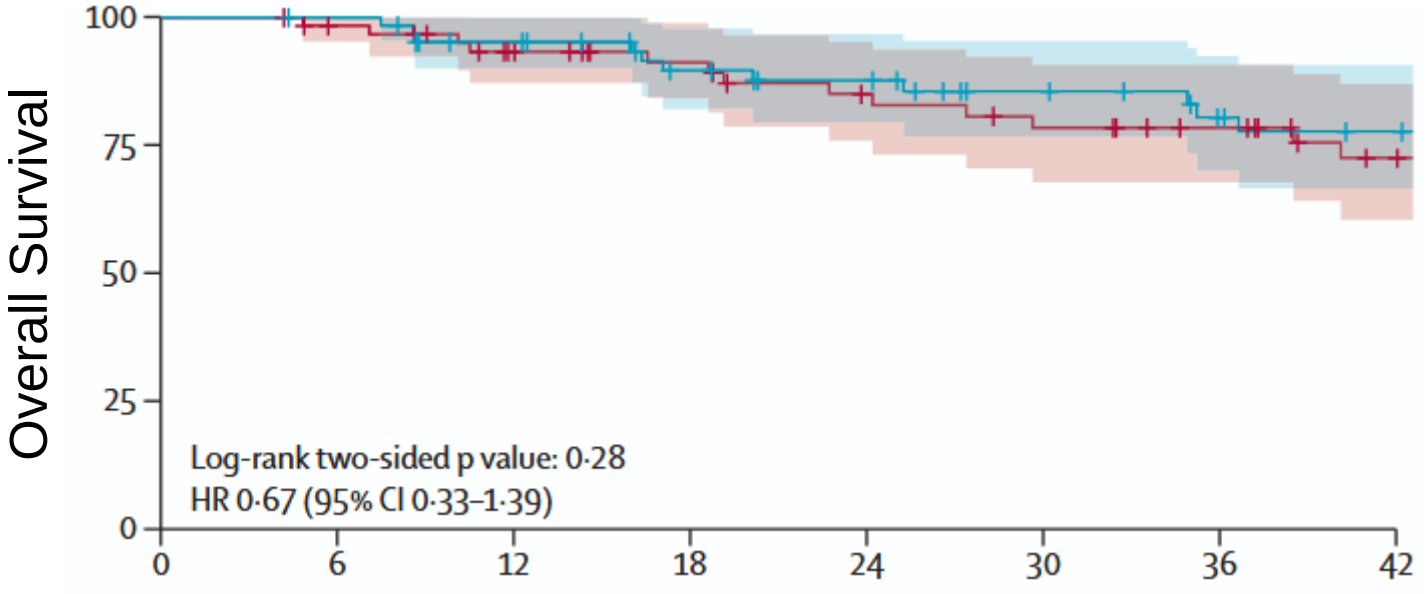
Actual enrollment

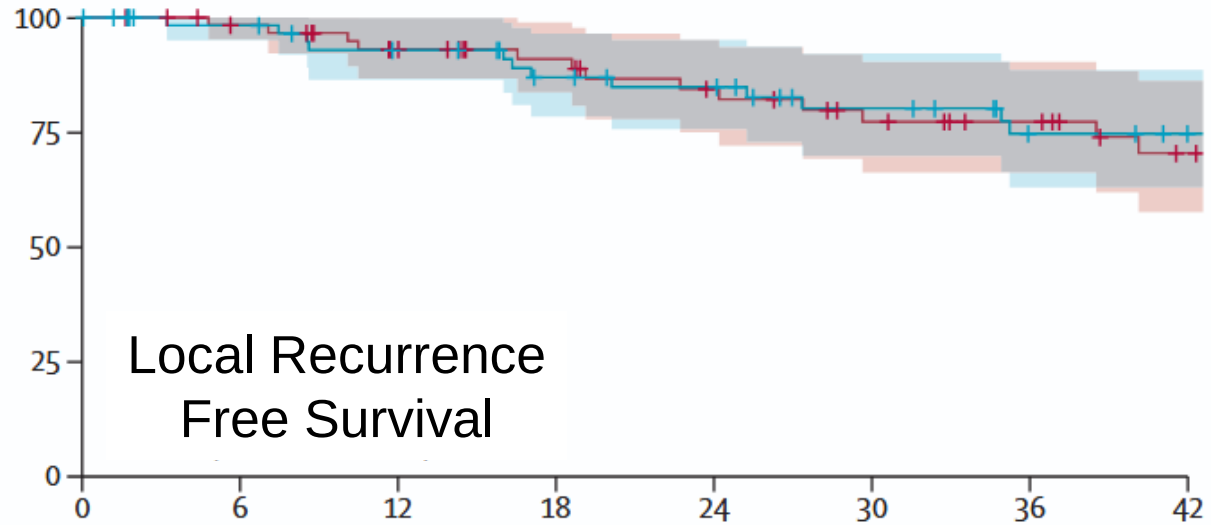
	Control group (n=63)	Experimental group (n=64)
Sarcoma histologic subtype at initial diagnosis		
Dedifferentiated liposarcoma	4 (6%)	4 (6%)
Pleomorphic liposarcoma	5 (8%)	0
Myxofibrosarcoma	6 (10%)	7 (11%)
Undifferentiated pleomorphic sarcoma	48 (76%)	53 (83%)

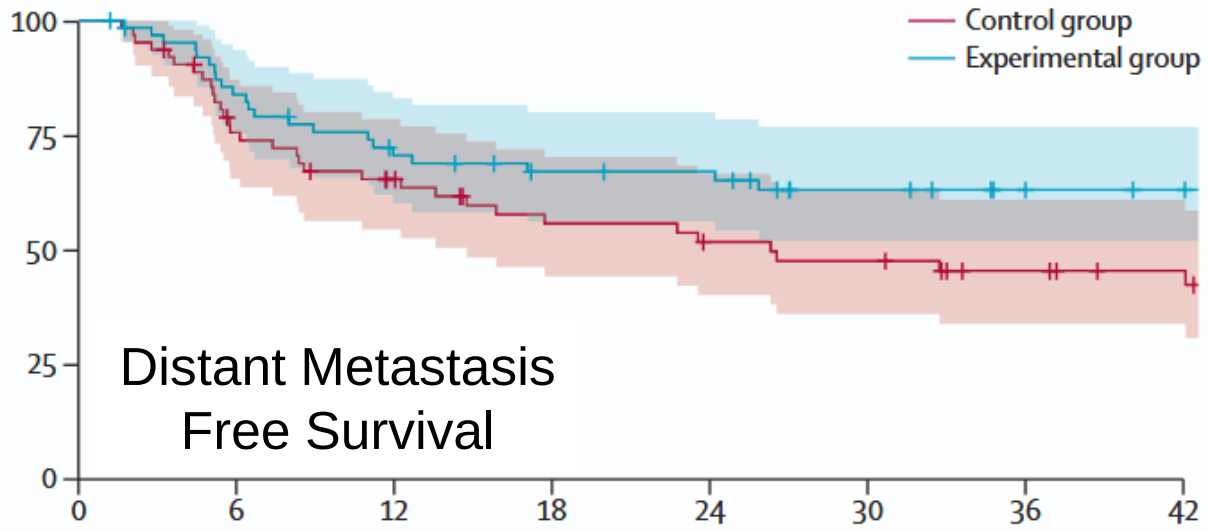
www.thelancet.com Published online November 12, 2024 https://doi.org/10.1016/S0140-6736(24)01812-9



www.thelancet.com Published online November 12, 2024 https://doi.org/10.1016/S0140-6736(24)01812-9

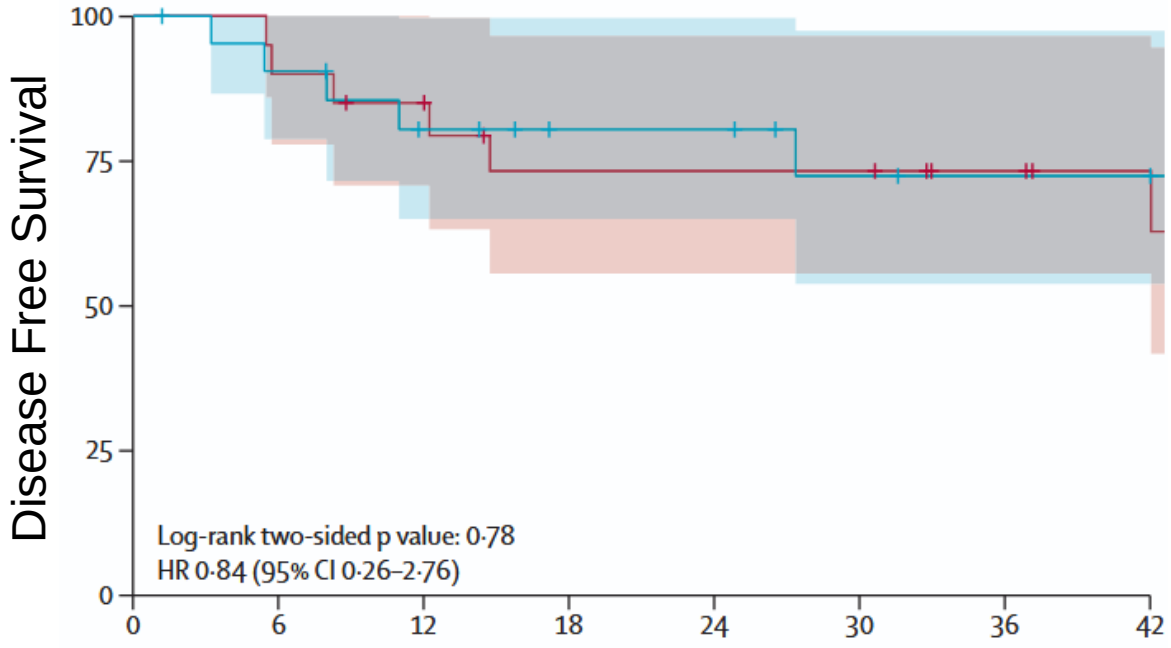




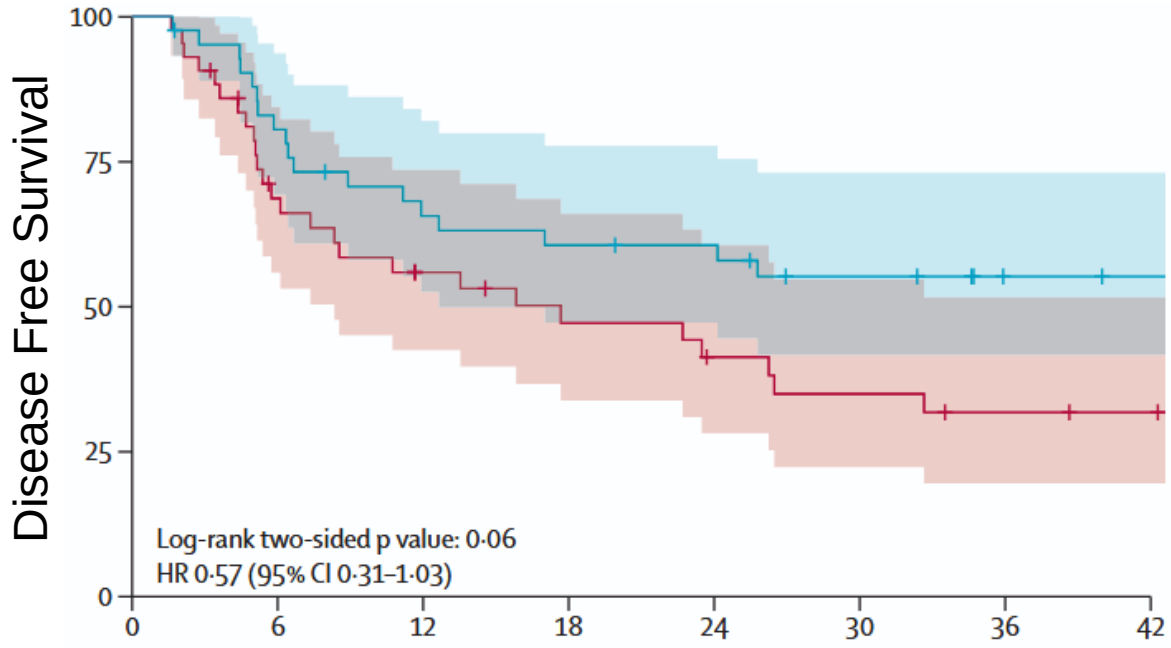


www.thelancet.com Published online November 12, 2024 https://doi.org/10.1016/S0140-6736(24)01812-9

Grade 2



Grade 3



www.thelancet.com Published online November 12, 2024 https://doi.org/10.1016/S0140-6736(24)01812-9

	RT + Resection	With Pembro
Any Grade 3/4	21/67 (31%)	39/70 (56%)

	Control group (n=67)				Experimental group (n=70)			
	Grades 1 and 2	Grade 3	Grade 4	Overall	Grades 1 and 2	Grade 3	Grade 4	Overall
Dermatitis radiation	26 (39%)	..	..	26 (39%)	34 (49%)	1 (1%)	..	35 (50%)
Fatigue	18 (27%)	..	..	18 (27%)	38 (54%)	1 (1%)	..	39 (56%)
Pain	13 (19%)	..	..	13 (19%)	13 (19%)	3 (4%)	..	16 (23%)
Nausea	6 (9%)	..	..	6 (9%)	19 (27%)	3 (4%)	..	22 (31%)
Pain in extremity	10 (15%)	..	..	10 (15%)	13 (19%)	2 (3%)	..	15 (21%)
Anaemia	4 (6%)	2 (3%)	..	6 (9%)	11 (16%)	7 (10%)	..	18 (26%)
Anorexia	7 (10%)	..	..	7 (10%)	13 (19%)	..	..	13 (19%)
Diarrhoea	..	1 (1%)	..	1 (1%)	17 (24%)	2 (3%)	..	19 (27%)
Edema limbs	8 (12%)	..	..	8 (12%)	10 (14%)	2 (3%)	..	12 (17%)
Wound infection	1 (1%)	6 (9%)	..	7 (10%)	6 (9%)	7 (10%)	..	13 (19%)
Constipation	4 (6%)	..	..	4 (6%)	15 (21%)	..	..	15 (21%)
Cough	2 (3%)	..	..	2 (3%)	15 (21%)	..	..	15 (21%)
Pruritus	2 (3%)	..	..	2 (3%)	14 (20%)	..	..	14 (20%)
Hypertension	3 (4%)	2 (3%)	1 (1%)	6 (9%)	3 (4%)	6 (9%)	..	9 (13%)
Hypothyroidism	..	..	..	..	14 (20%)	1 (1%)	..	15 (21%)
Rash maculo-papular	..	..	..	..	15 (21%)	..	..	15 (21%)

Takeaways

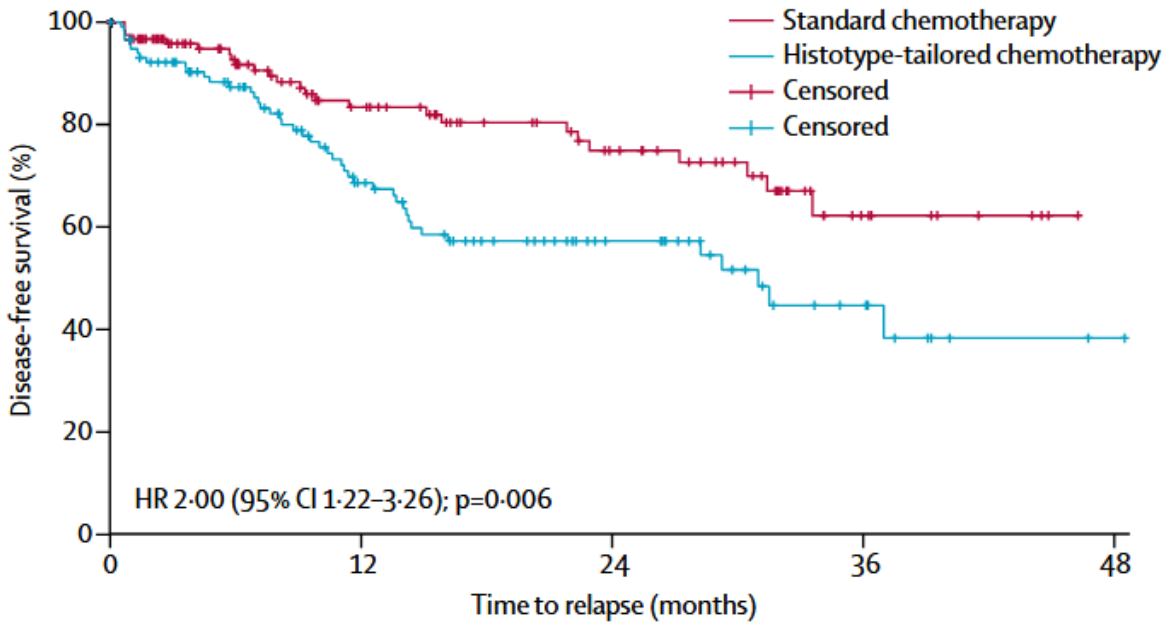
Pembrolizumab with neoadjuvant radiation is an option for grade 3 extremity Undifferentiated Pleomorphic Sarcoma (and similar entities including myxofibrosarcoma) based on Disease Free Survival

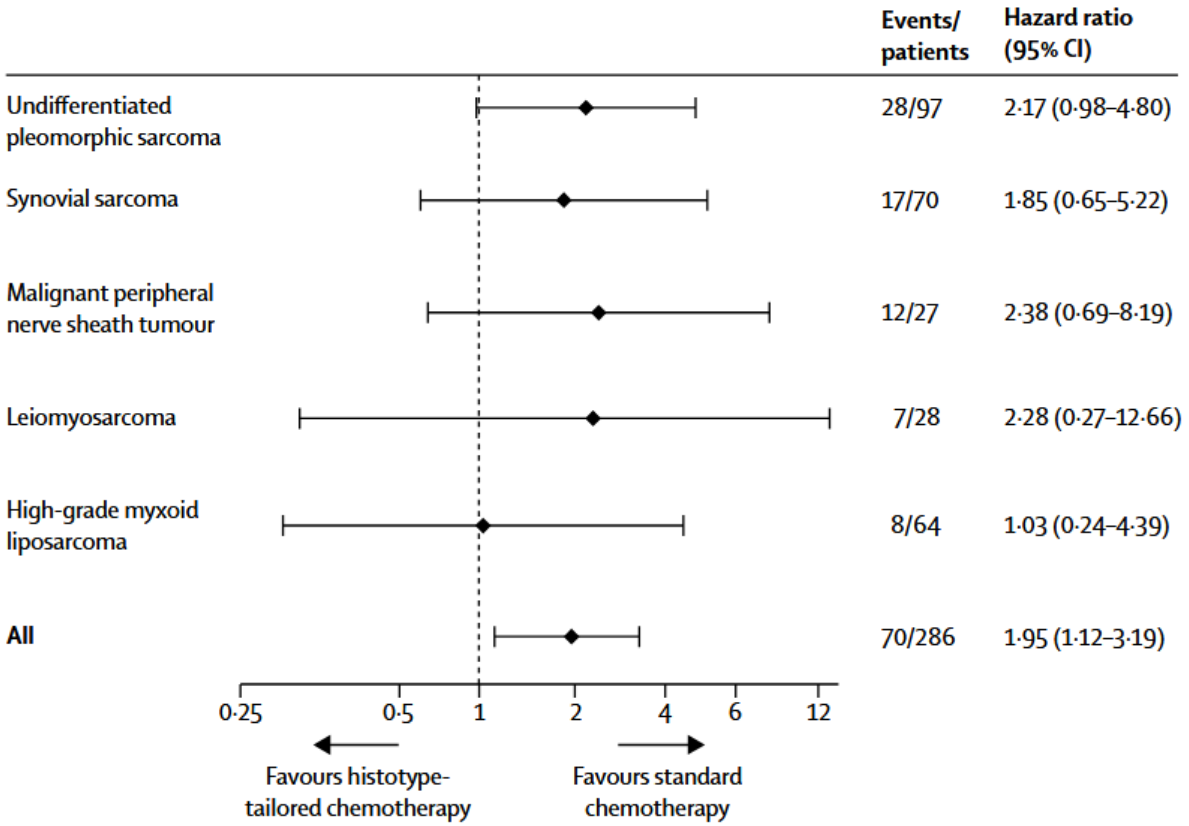
Might not be applicable to grade 2, or liposarcoma

AIM is also still an option for patients <65-70 years if fit

Histiotype tailored neoadjuvant therapy

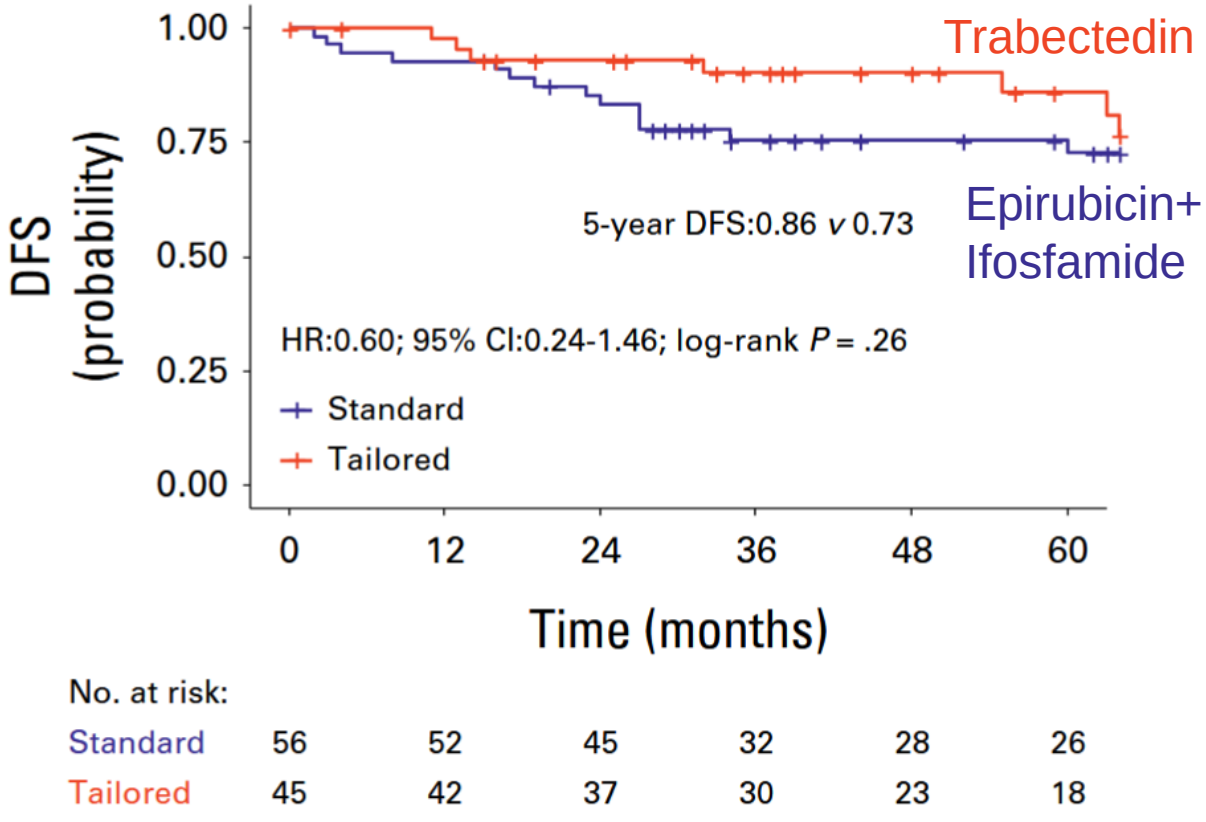
Standard:	Epirubicin + Ifosfamide
UPS:	Gemcitabine + Docetaxel
Synovial sarcoma:	Ifosfamide continuous infusion
MPNST:	Ifosfamide + Etoposide
Leiomyosarcoma:	Gemcitabine + Dacarbazine
Myxoid liposarcoma:	Trabectedin

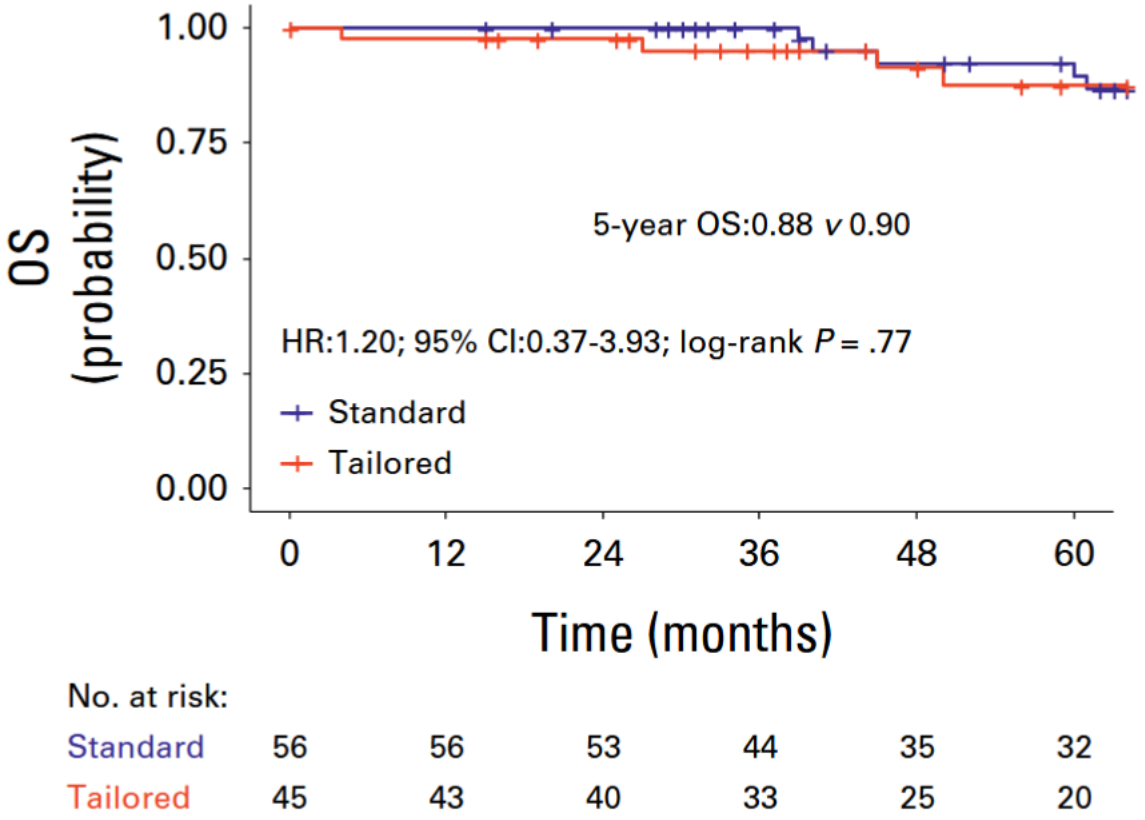




Lancet Oncol 2017; 18: 812–22

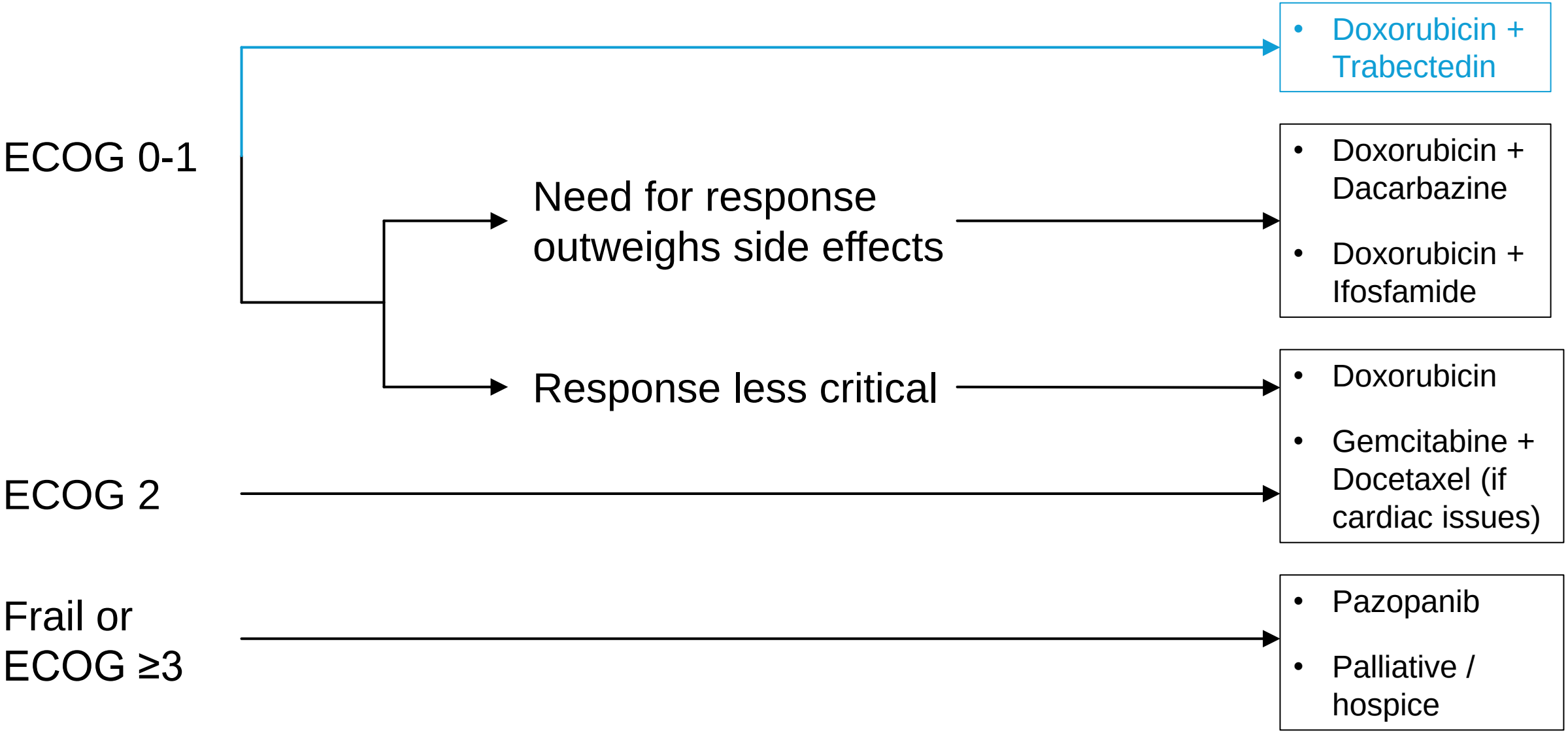
Myxoid Liposarcoma expansion cohort





J Clin Oncol 42:898-906

Unresectable leiomyosarcoma: Early 2024 vs 2025



Doxorubicin–Trabectedin with Trabectedin Maintenance in Leiomyosarcoma

P. Pautier, A. Italiano, S. Piperno-Neumann, C. Chevreau, N. Penel, N. Firmin, P. Boudou-Rouquette, F. Bertucci, V. Lebrun-Ly, I. Ray-Coquard, E. Kalbacher, E. Bompas, O. Collard, N. Isambert, C. Guillemet, M. Rios, A. Le Cesne, C. Balleyguier, B. Archambaud, and F. Duffaud, for the French Sarcoma Group*

First line unresectable / metastatic leiomyosarcoma

6 cycles Doxorubicin (60 mg/m^2)
Trabectedin (1.1 mg/m^2)

Then Trabectedin (1.1 mg/m^2)

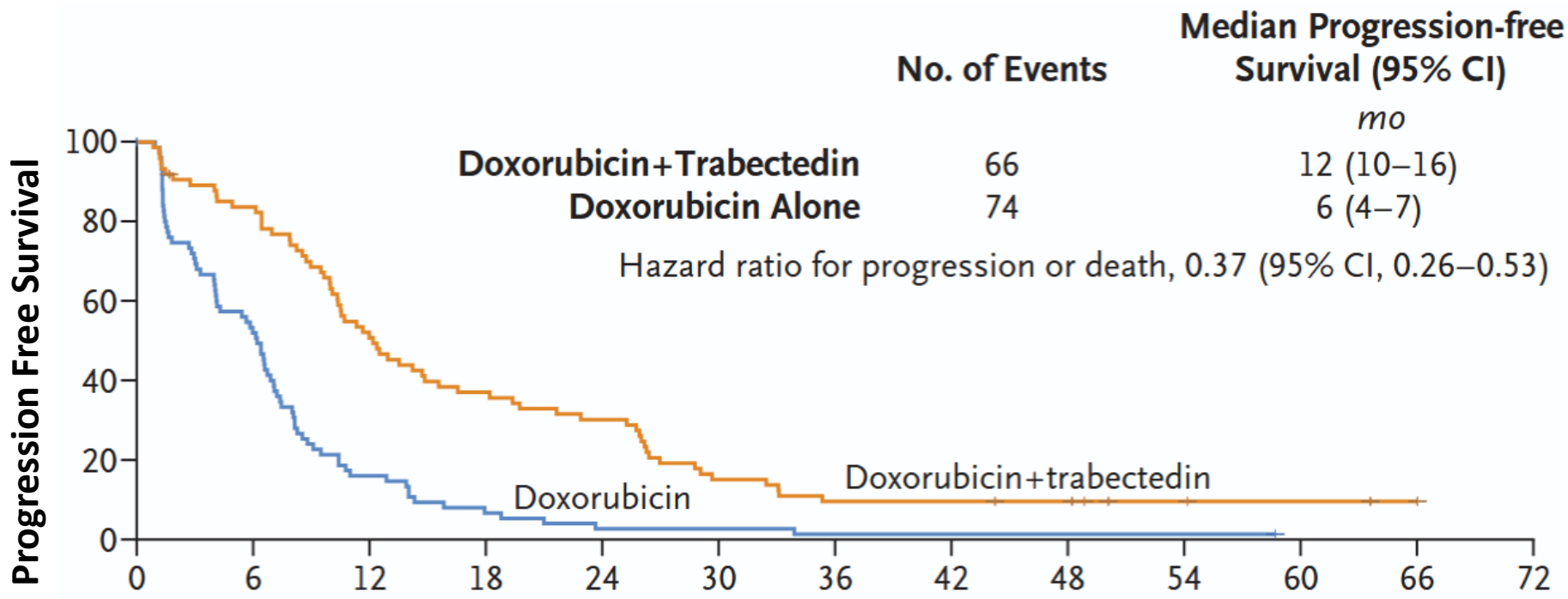
versus

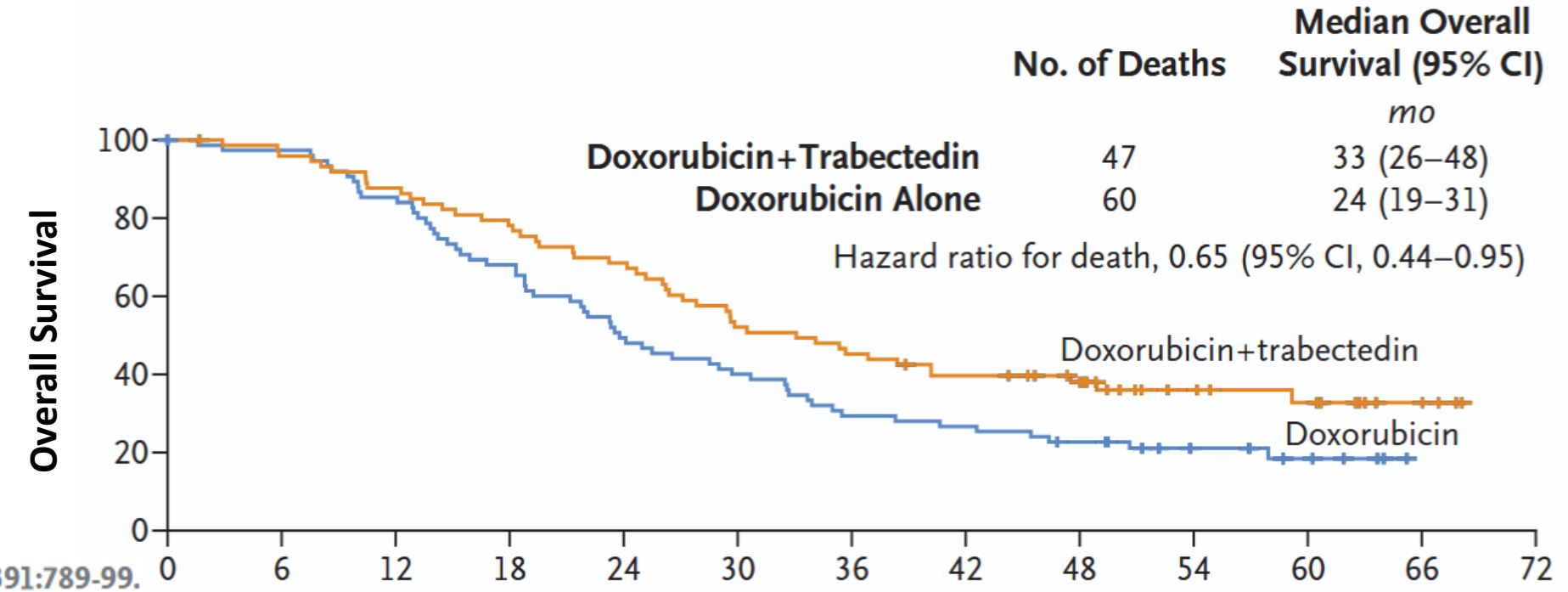
6 cycles Doxorubicin (75 mg/m^2)

Table 1. Characteristics of the Patients.*

Characteristic	Doxorubicin Alone (N=76)	Doxorubicin + Trabectedin (N=74)
Median age (range) — yr	64 (53–69)	59 (52–68)
Female sex — no. (%)	59 (78)	53 (72)
ECOG performance-status score — no./total no. (%)†		
0	45/74 (61)	47/70 (67)
1	29/74 (39)	23/70 (33)
Disease grade — no./total no. (%)‡		
1	8/42 (19)	11/41 (27)
2	16/42 (38)	11/41 (27)
3	10/42 (24)	12/41 (29)
Missing data	8/42 (19)	7/41 (17)
Site of primary tumor — no. (%)		
Uterus	34 (45)	33 (45)
Soft tissue	42 (55)	41 (55)

N Engl J Med 2024;391:789-99.





N Engl J Med 2024;391:789-99.

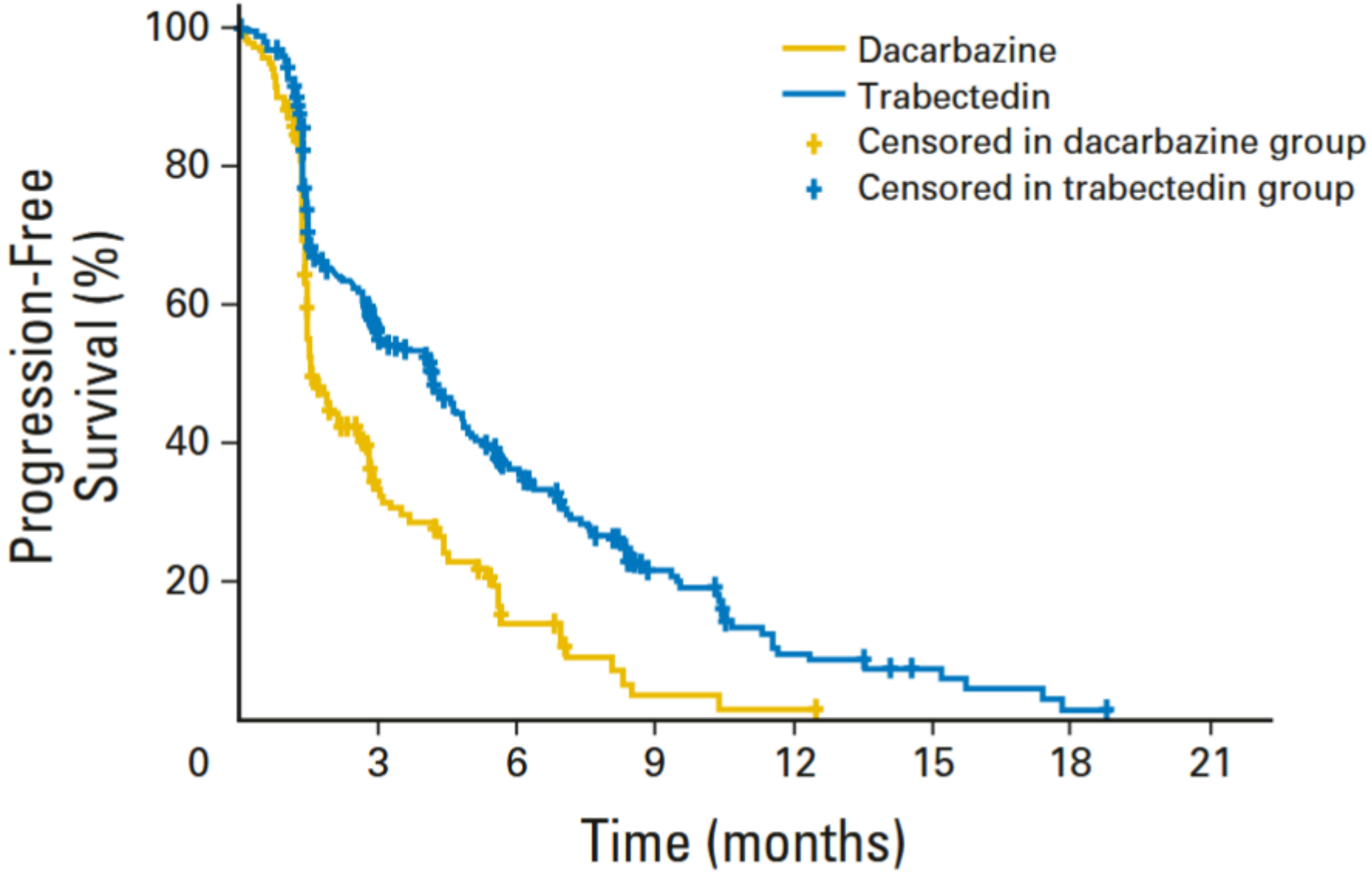
LMS-04 trial

	Doxorubicin	Doxorubicin + Trabectedin
CR	0	3/74 (4%)
CR+PR	10/76 (13%)	27/74 (36%)
Uterine	5/34 (15%)	12/33 (36%)
Non-uterine	5/42 (12%)	15/41 (37%)

EORTC retrospective data - First line leiomyosarcoma

	Doxorubicin	Doxorubicin + Ifosfamide	Doxorubicin + Dacarbazine
CR+PR	26%	20%	31%

Lancet Oncol 2022; 23: 1044–54



J Clin Oncol 34:786-793.

	Doxorubicin alone group (n=75)				Doxorubicin and trabectedin group (n=74)			
	Grade 1–2*	Grade 3	Grade4	Grade 5	Grade 1–2*	Grade 3	Grade 4	Grade 5
Anaemia	55 (73%)	0	4 (5%)	0	51 (69%)	20 (27%)	3 (4%)	0
Febrile neutropenia	3 (4%)	4 (5%)	3 (4%)	0	5 (7%)	7 (9%)	14 (19%)	0
Leukopenia	24 (32%)	2 (3%)	1 (1%)	0	10 (14%)	24 (32%)	32 (43%)	0
Lymphopenia	0	1 (1%)	0	0		4 (5%)	0	0
Neutropenia	20 (27%)	7 (9%)	3 (4%)	0	5 (7%)	14 (19%)	45 (61%)	0
Thrombocytopenia	6 (8%)	0	0	0	24 (32%)	17 (23%)	18 (24%)	0
Cardiac failure	0	1 (1%)	1 (1%)	1 (1%)	0	1 (1%)	0	0
Dyspnoea	9 (12%)	1 (1%)	0	0	10 (14%)	1 (1%)	0	0
Constipation	17 (23%)	1 (1%)	0	0	28 (38%)	1 (1%)	0	0
Diarrhoea	10 (13%)	1 (1%)	0	0	26 (35%)	2 (3%)	0	0
Dysgeusia	10 (13%)	0	0	0	10 (14%)	0	0	0
Enteritis	0	0	0	0	0	1 (1%)	0	0
Faecaloma	0	0	0	0	0	0	1 (1%)	0
Intestinal obstruction	0	1 (1%)	0	0	0	1 (1%)	0	0
Nausea	46 (61%)	1 (1%)	0	0	59 (80%)	5 (7%)	0	0
Vomiting	10 (13%)	0	0	0	59 (80%)	4 (5%)	0	0

Lancet Oncol 2022; 23: 1044–54

Takeaways

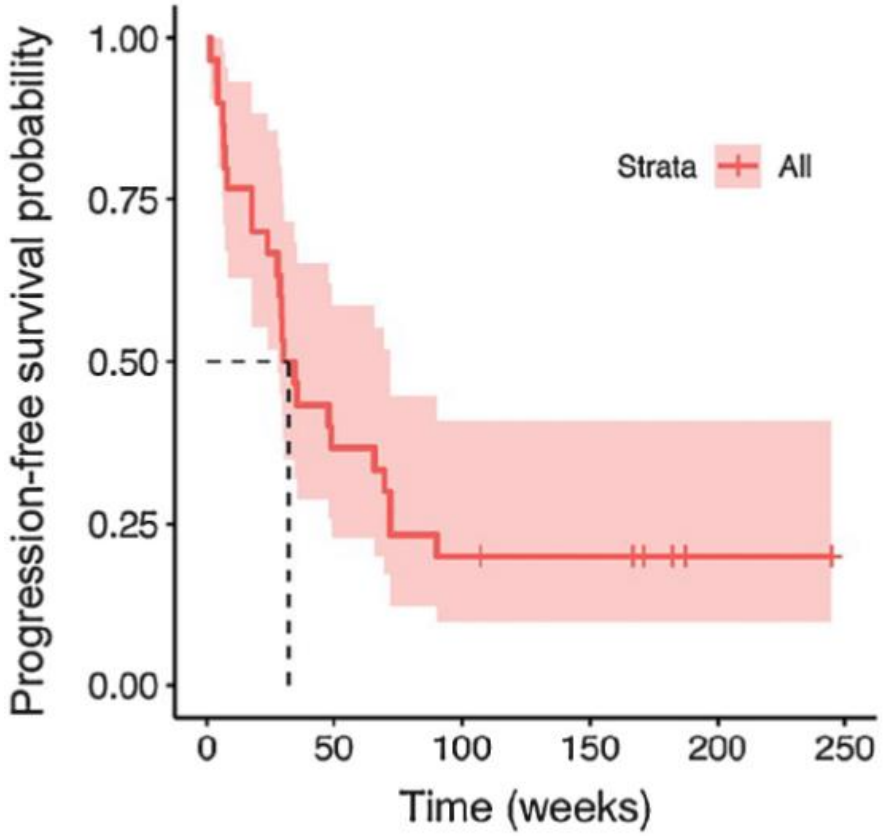
Doxorubicin + trabectedin now the preferred approach for fit unresectable leiomyosarcoma patients

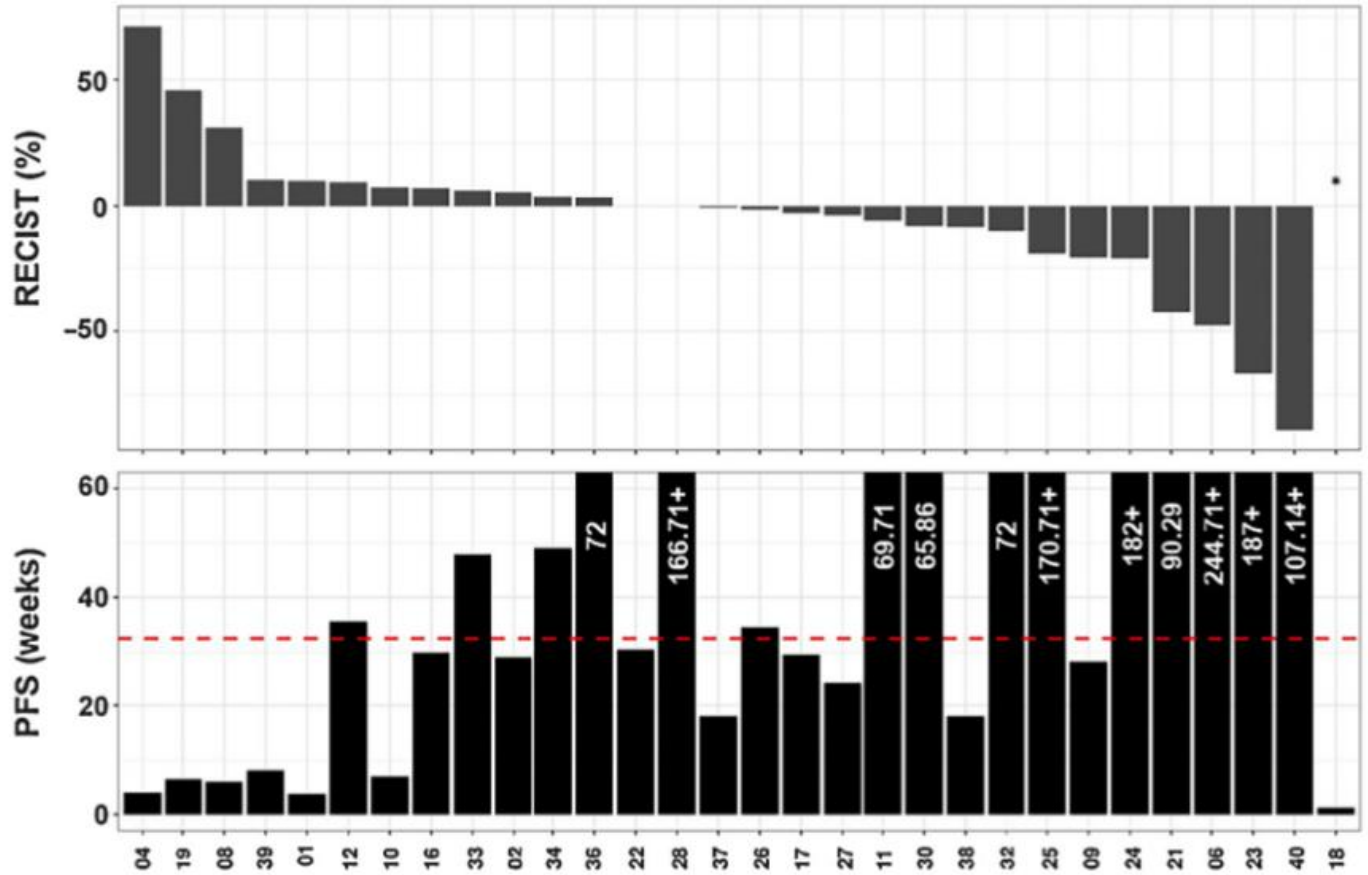
Applicable to uterine and extrauterine

No data on neoadjuvant / adjuvant at this point

Unresectable dedifferentiated liposarcoma

Strongly associated with amplification of CDK4 and MDM2
Abemaciclib: mPFS 33 weeks, 15/30 patients after first line
Doxorubicin: mPFS 31 weeks, all first line in Brightline-1 trial (CTOS 2024)





Gleason et al. Clin Cancer Res. 2024 Feb 16;30(4):703-718.

Synovial sarcoma

Afami-cel (afamitresgene autoleucel)
TCR-T cell targeting MAGE-A4

Must have MAGE-A4 expression (on tissue) and compatible HLA type

Testing available through https://www.tecelra-hcp.com

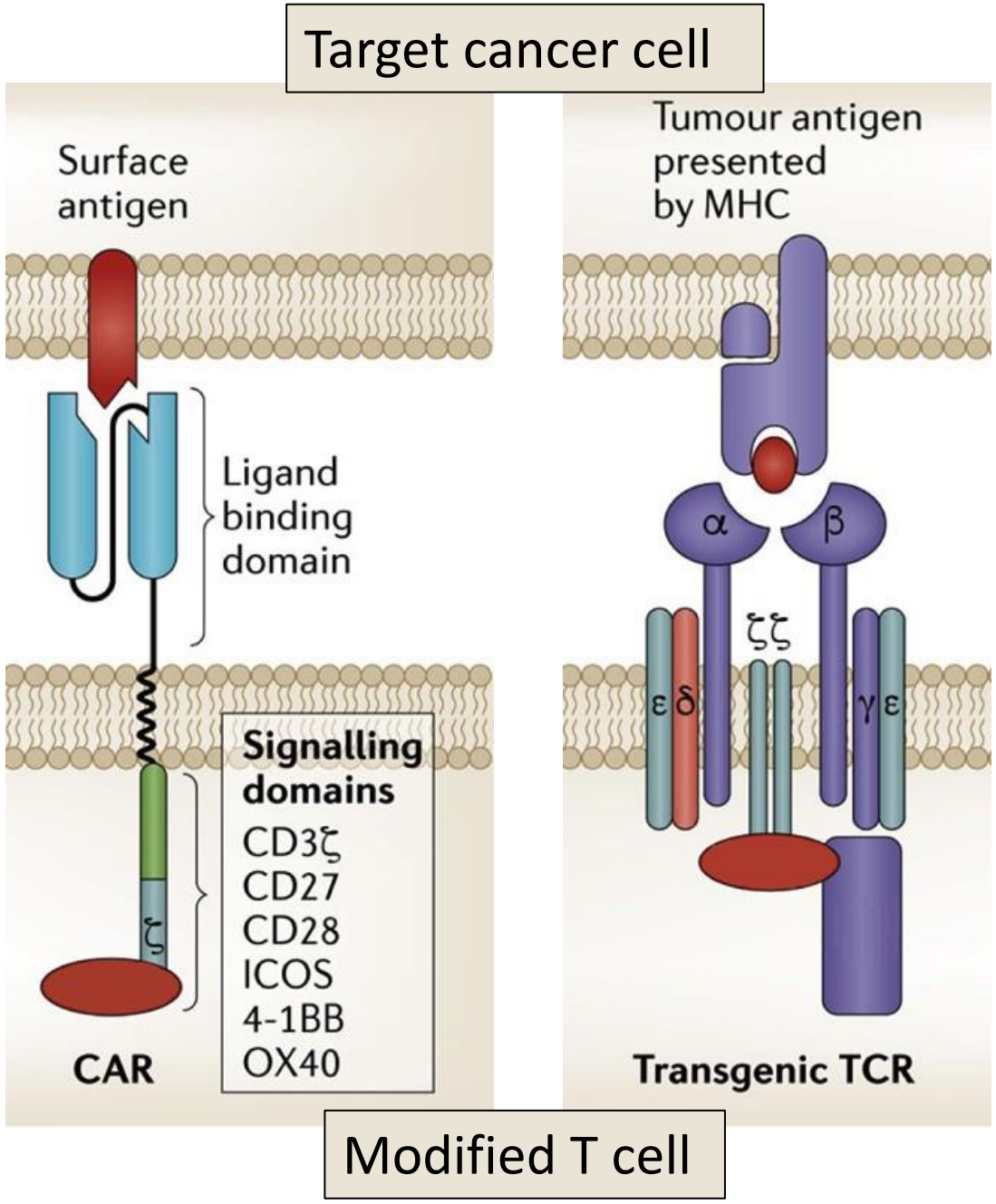
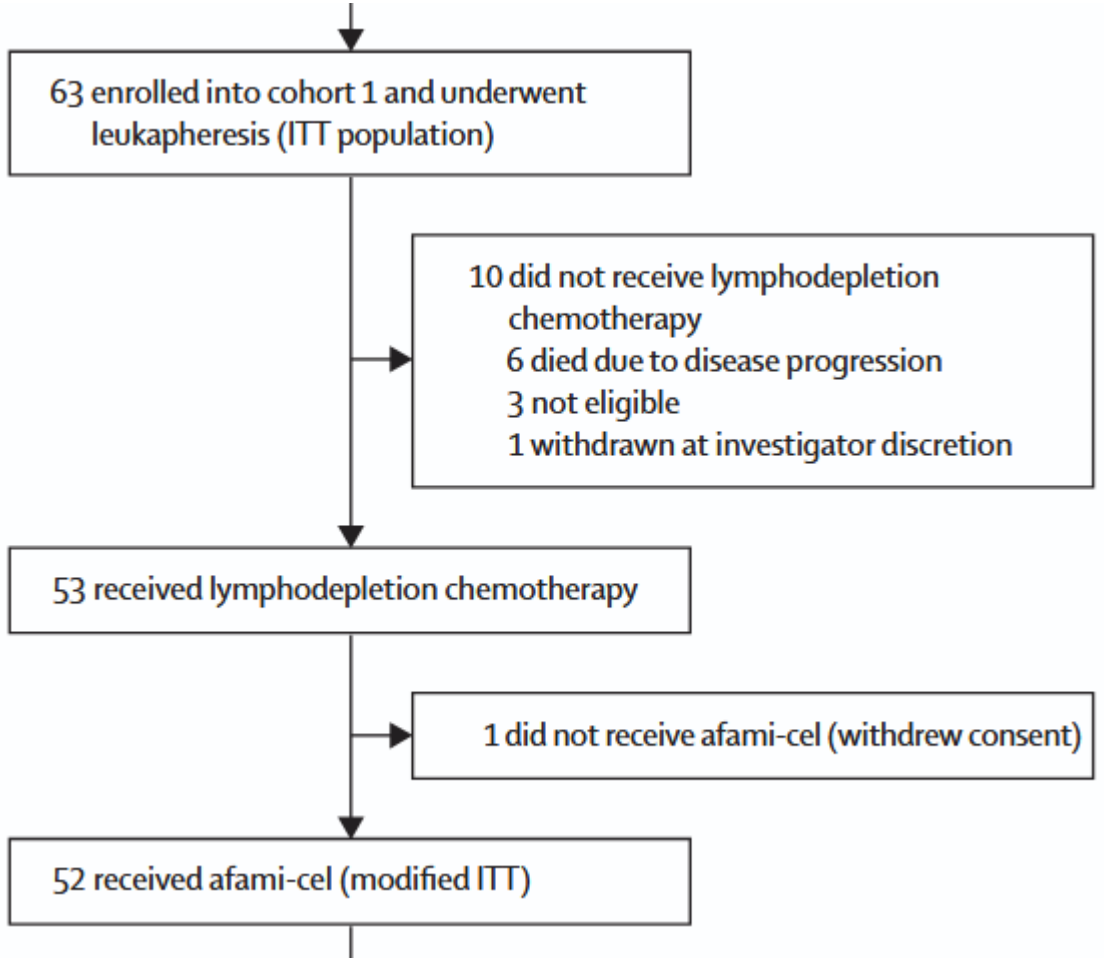


Image: Garber, K. Driving T-cell immunotherapy to solid tumors. Nat Biotechnol 36, 215–219 (2018).

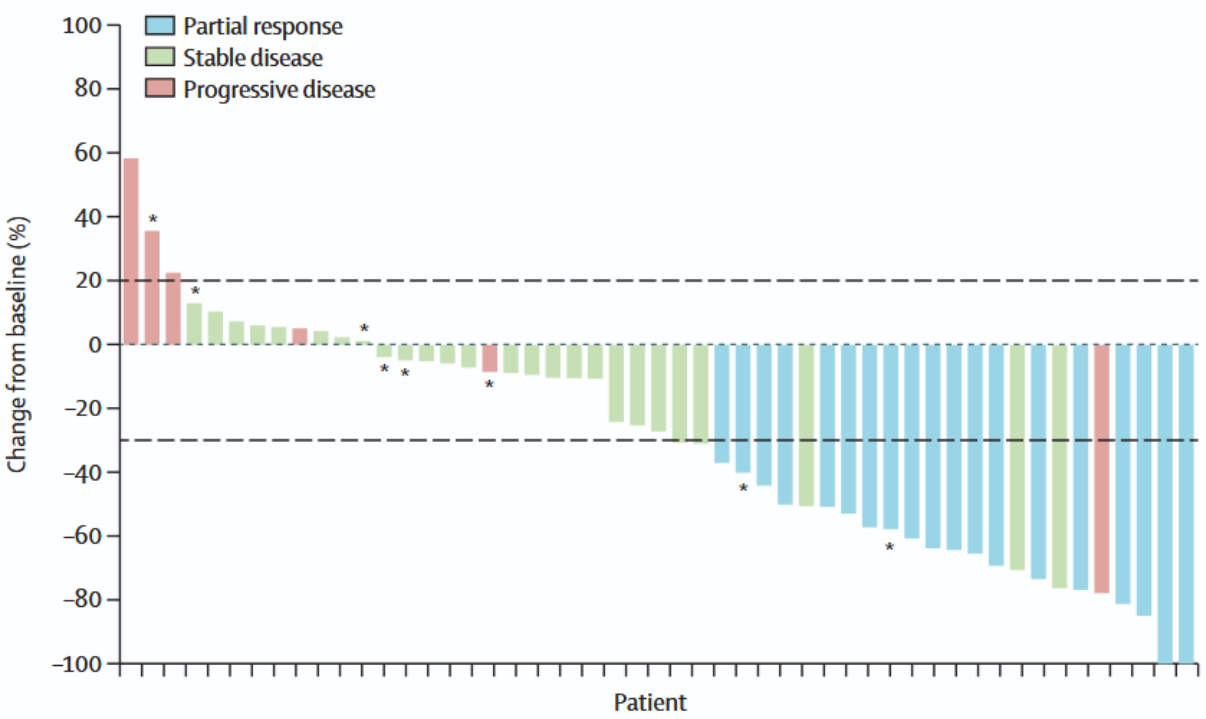
Afamitresgene autoleucel for advanced synovial sarcoma and myxoid round cell liposarcoma (SPEARHEAD-1): an international, open-label, phase 2 trial

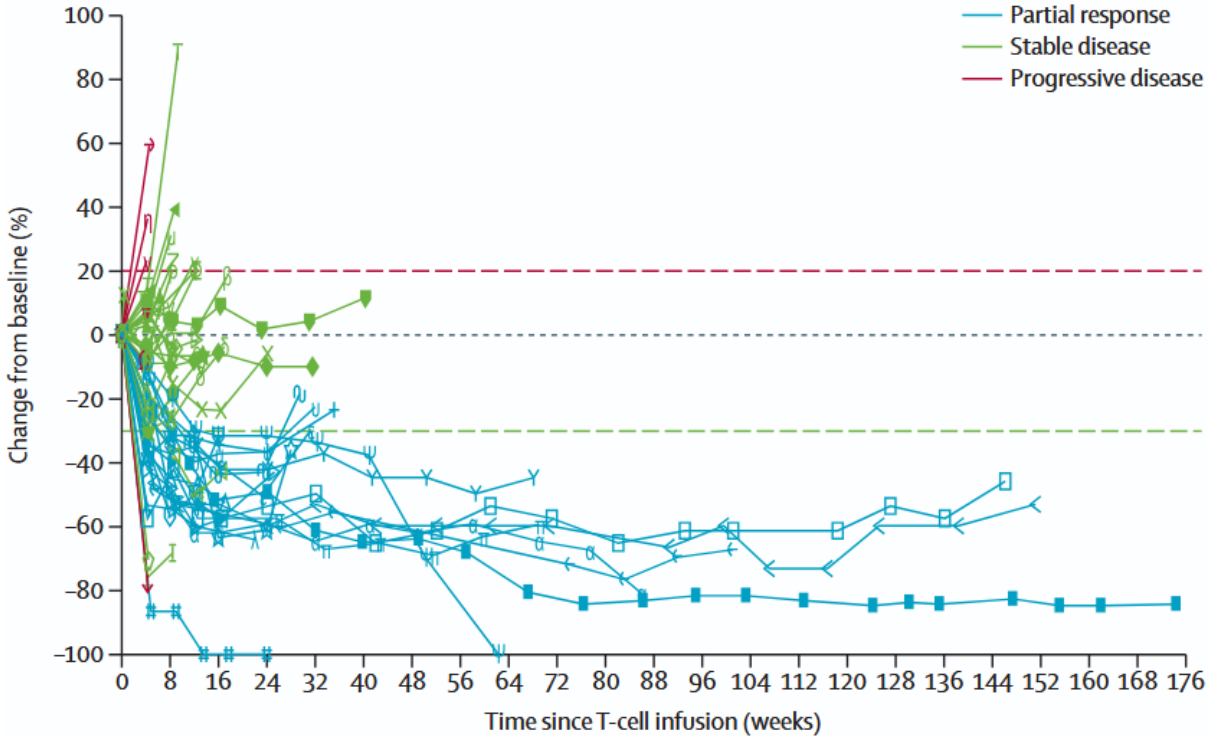
Synovial sarcoma or myxoid liposarcoma
After doxorubicin and/or ifosfamide
MAGE-A4 positive and compatible MHC
(28% of screened patients)

Leukapheresis
± Bridging therapy (~7 weeks)
Flu-Cy conditioning and T cell infusion
No IL-2 or other cytokines

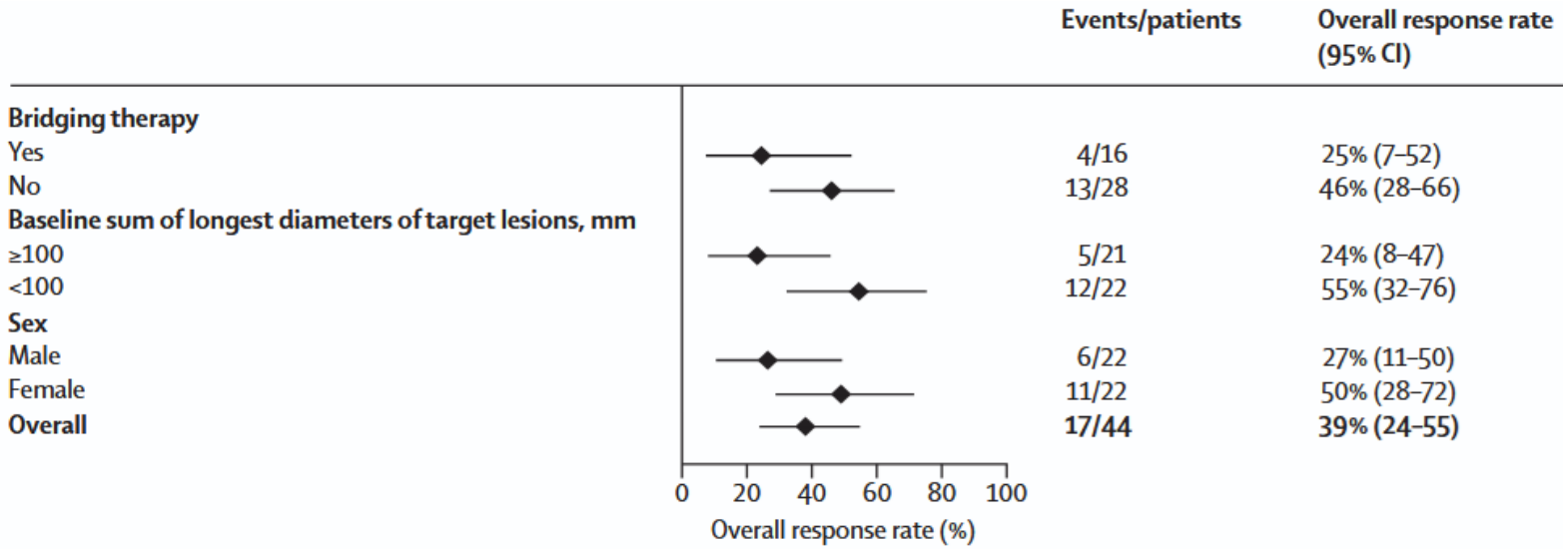


Lancet 2024; 403: 1460–71

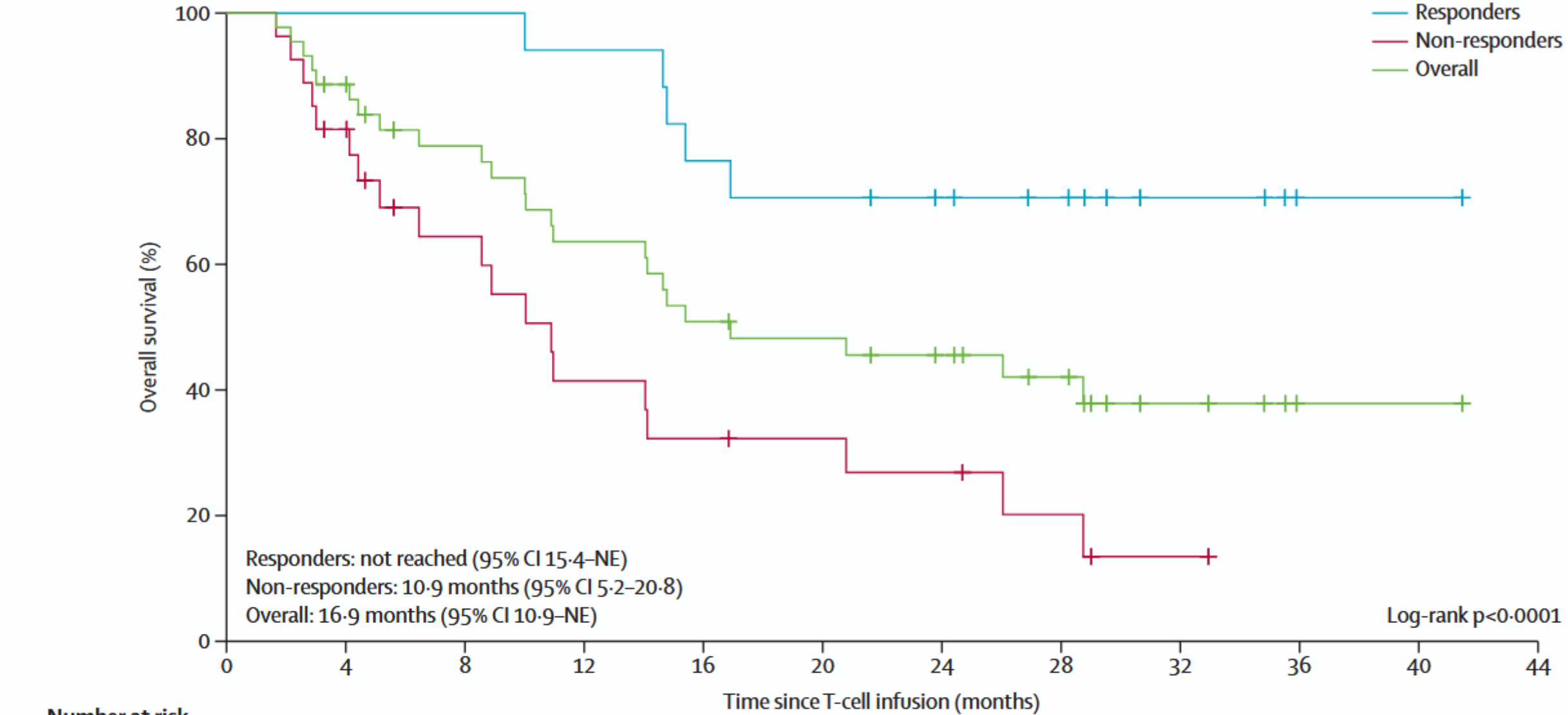




Asterisks – myxoid liposarcoma
39% ORR in synovial sarcoma



Lancet 2024; 403: 1460–71



Number at risk (number censored)												
Responders	17 (0)	17 (0)	17 (0)	16 (0)	13 (0)	12 (0)	10 (2)	8 (4)	4 (8)	1 (11)	1 (11)	0 (12)
Non-responders	27 (0)	21 (1)	14 (4)	9 (4)	7 (4)	6 (5)	5 (5)	3 (6)	1 (7)	0 (8)	..	..
Overall	44 (0)	38 (1)	31 (4)	25 (4)	20 (4)	18 (5)	15 (7)	11 (10)	5 (15)	1 (19)	1 (19)	0 (20)

Lancet 2024; 403: 1460–71

CRS: low grade was common, grade 3 in 1 patient
ICANS: grade 1 in 1 patient, resolved in 1 day
Cytopenias >1 month: 11% neutropenia
9% anemia
5% thrombocytopenia

Daily (likely inpatient) monitoring for 1 week, then closely for 1 month

	Grade 1–2	Grade 3	Grade 4	Overall
Cytokine release syndrome	36 (69%)	1 (2%)	0	37 (71%)
Decreased white blood cell count or leukopenia	1 (2%)	8 (15%)	5 (10%)	14 (27%)
Pyrexia	10 (19%)	1 (2%)	1 (2%)	12 (23%)
Decreased neutrophil count or neutropenia	1 (2%)	5 (10%)	6 (12%)	12 (23%)
Decreased lymphocyte count or lymphopenia	0	3 (6%)	6 (12%)	9 (17%)
Nausea	6 (12%)	0	0	6 (12%)
Fatigue	6 (12%)	0	0	6 (12%)
Decreased platelet count or thrombocytopenia	3 (6%)	1 (2%)	2 (4%)	6 (12%)
Weight loss	2 (4%)	1 (2%)	0	3 (6%)
Febrile neutropenia	1 (2%)	2 (4%)	0	3 (6%)

Lancet 2024; 403: 1460–71

Takeaways

Afami-cel is an option in HLA compatible and MAGE-A4 expressing synovial sarcoma with possibility of durable benefit from a single treatment

Modest CRS and ICANS compared to CAR-T

Long lead time for testing, referral, leukapheresis, and administration

Summary

Perioperative

- Undifferentiated Pleomorphic Sarcoma / Myxofibrosarcoma – Pembro
- Myxoid Liposarcoma – Trabectedin

Unresectable

- Leiomyosarcoma – Doxorubicin + Trabectedin
- Dedifferentiated Liposarcoma – Abemaciclib

Later line of therapy

- Synovial Sarcoma – Afami cel