LIFEFEST2026

Nashville

LIPOSARCOMA 101

Dr. Breelyn Wilky

University of Colorado
Anschutz Medical Campus

University of Colorado **Anschutz Medical Campus**

Liposarcoma 101

Breelyn A. Wilky, MD

Disclosures

- **Consulting/Advisory Role**

  AADI, Adcendo, Boehringer Ingelheim, Deciphera,Inhibrx, Parabilis, Springworks

- **Research Funding**

  Agenus, Exelixis

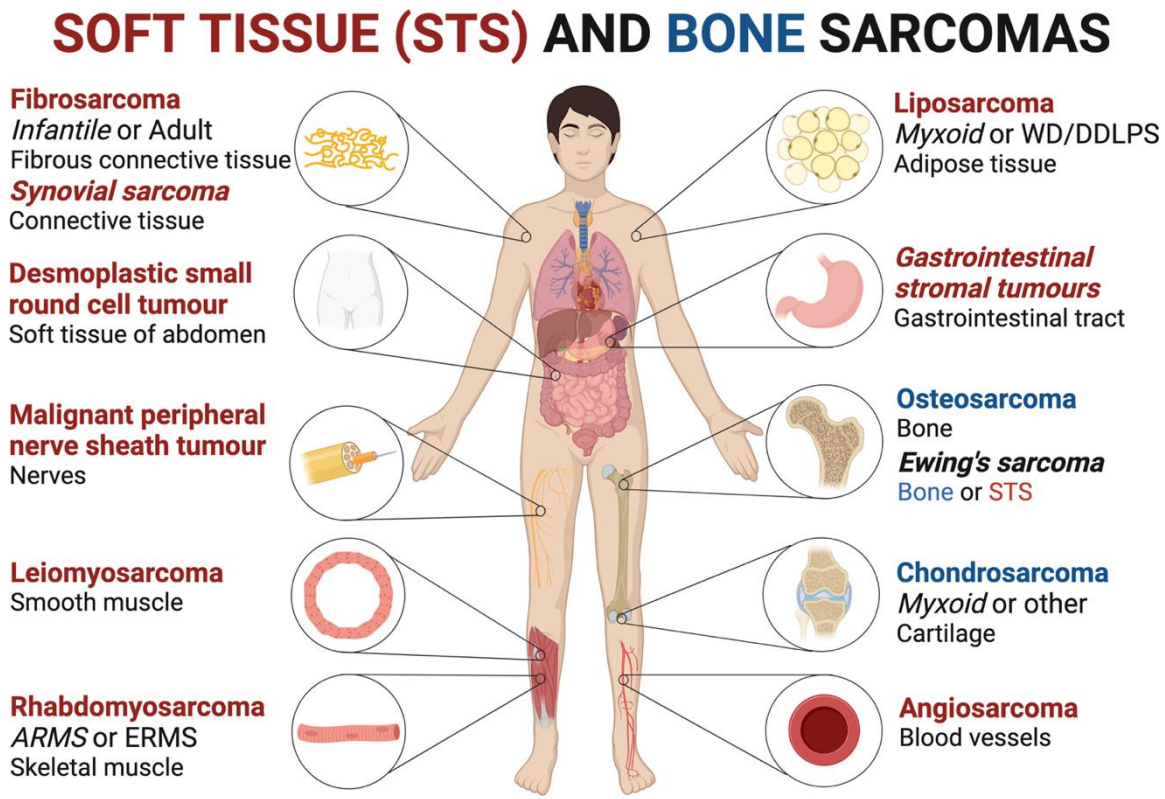
Overview – Liposarcoma 101

- Liposarcoma – basics of the disease
- A few cases to set the stage
- The treatment journey and options along the way

- Lots of time for questions!

What is liposarcoma?

- 100+ different histologic subtypes of bone and soft tissue neoplasms (but 1% of adult cancer!)
- Liposarcomas arise from fat cells
- 4 different kinds!
  - Well differentiated liposarcoma
  - Dedifferentiated liposarcoma
  - Myxoid/round cell liposarcoma
  - Pleomorphic liposarcoma



High-grade undifferentiated pleomorphic sarcomas (UPS) – mesenchymal stem cells

Wilky et al, ASCO SEP 2022

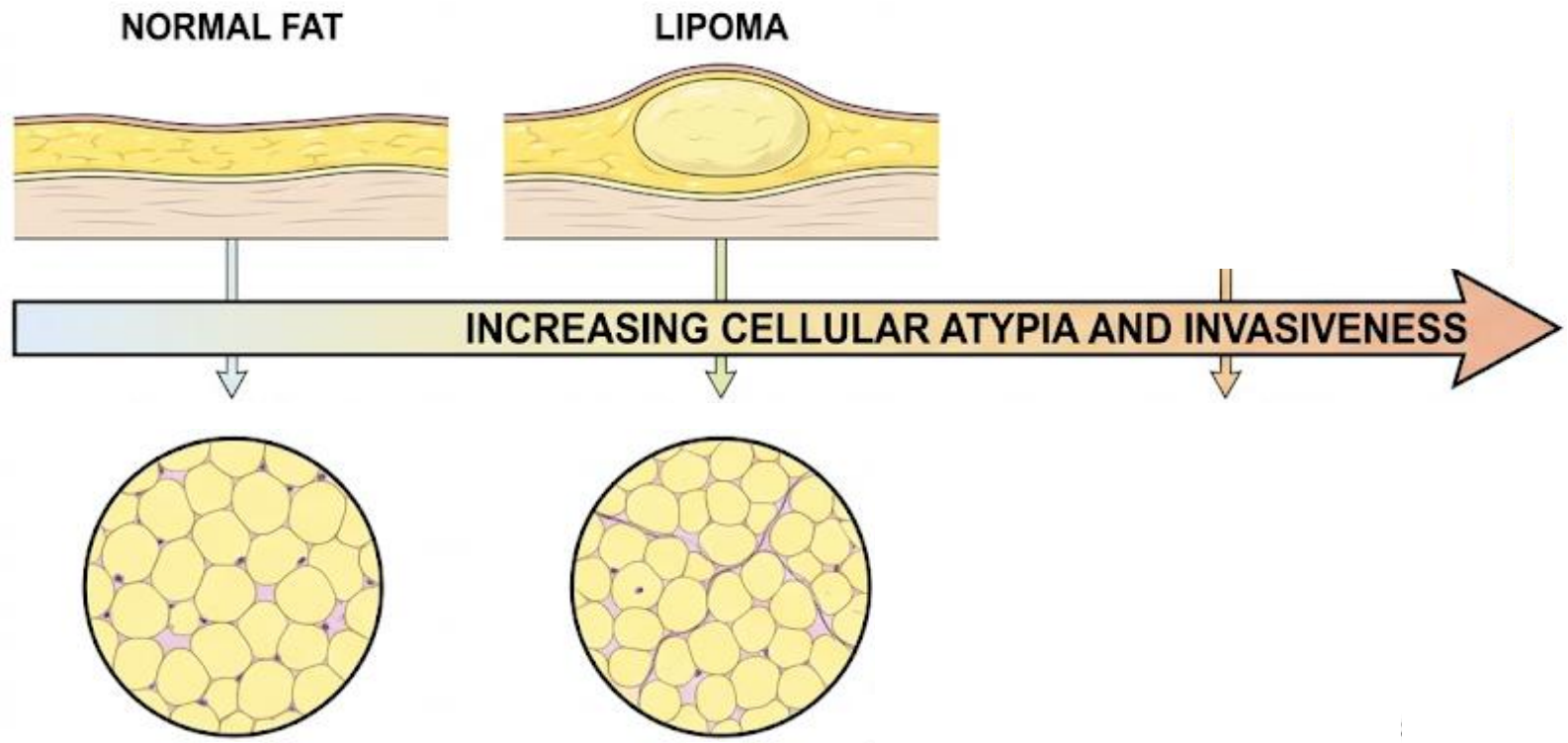
What is liposarcoma?

- One of the most common subtypes in adults – peak age 50-65 (myxoid younger patients, pleomorphic older patients)
- Most are sporadic, with few identified risk factors
  - Not associated with obesity or diet
  - Prior radiation, military exposures
  - Few inherited syndromes but possibly in Li-Fraumeni and retinoblastoma
- Location: Extremities (myxoid, pleomorphic) and retroperitoneum (well-diff/dediff)
- Metastatic sites: lung, liver, bone (less common in retroperitoneal)
- Symptoms: depends on location – palpable mass in extremities, or vague symptoms in abdominal locations (early satiety, weight gain/abdominal distension, bloating)

Menon & Kaur, StatPearls 2026

The fat continuum….

Atypical lipomatous tumor



Enlarging mature fat cells
Overexpression of HMGA2 (translocations)
Benign

Amplification of 12q13-15
MDM2/CDK4
Always low grade

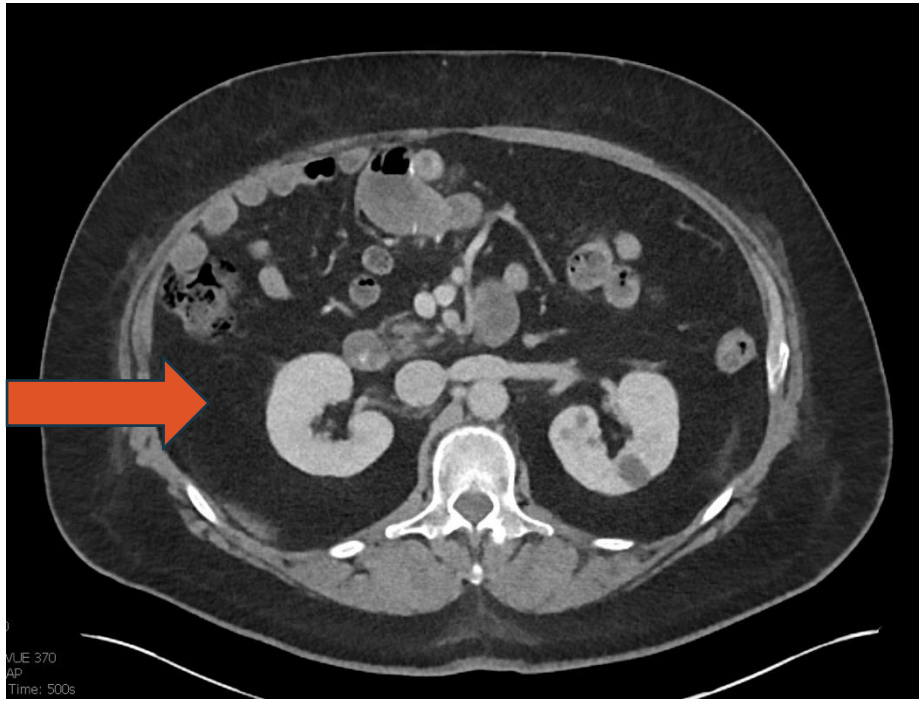
Additional genetic chaos
Loss of p53, RB1
Grade 1 – 3 spectrum

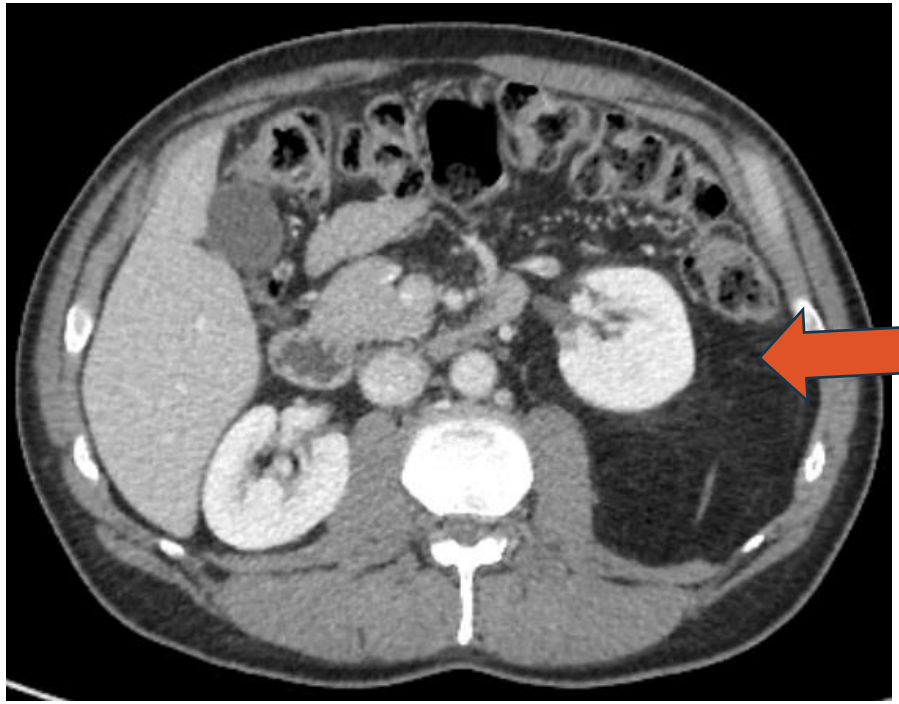
Made with assistance from Google Gemini

Diagnosing liposarcoma

- Can be tricky to diagnose on scans because well-diffs can look like normal fat – really need contrast-enhanced MRI or CT
- Look for fat “stranding” and subtle “septae” between fat globules
- Looks like normal fat intraoperatively! (except large mass or size)

Normal fat





Abnormal fat

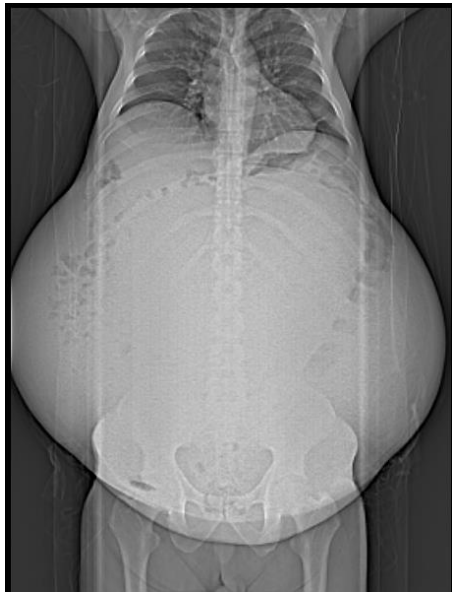
Myxoid/round cell and pleomorphic LPS

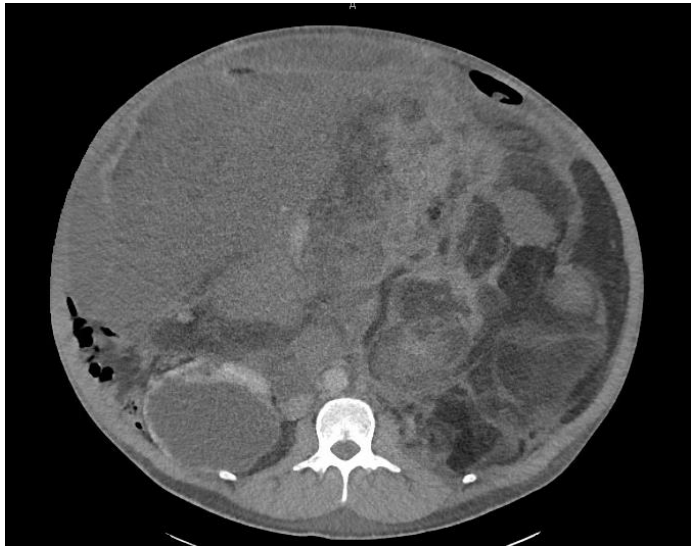
- **Myxoid** (low grade) can have a high grade component (**round cell**)
- Characterized by conserved CHOP (DDIT3) translocations
  - FUS-DDIT3 (90-95%) and EWSR1-DDIT3 (5%) transcription factors drive abnormal lipoblasts
  - Round cell acquires TERT, PIK3CA, mutations among others
- **Pleomorphic** (high grade) – highly complex genetics
  - Lipoblasts visible
  - NO amplification of MDM2/CDK4
  - Deletions of p53, RB1, NF1
  - Polyploidy, copy number alterations

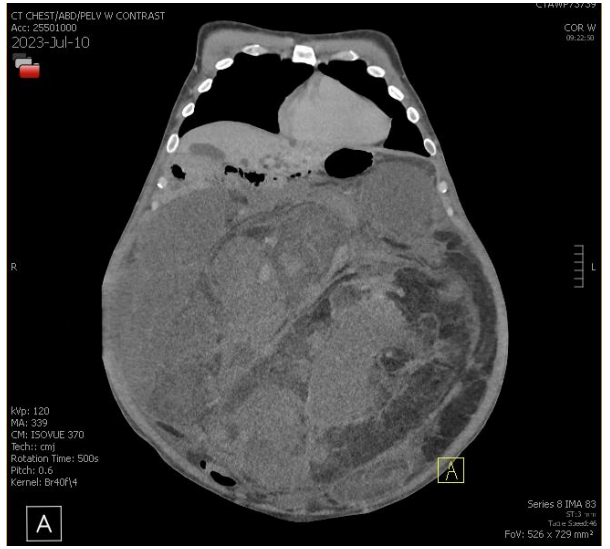
Case examples

Retroperitoneal liposarcoma (well-diff/dediff)

- 38 yo M with history of polycystic kidney disease who presented with several month history of weight gain/enlarging abdomen
- Some lower extremity swelling he attributed to an ankle injury
- Saw PCP who was concerned and ordered scans

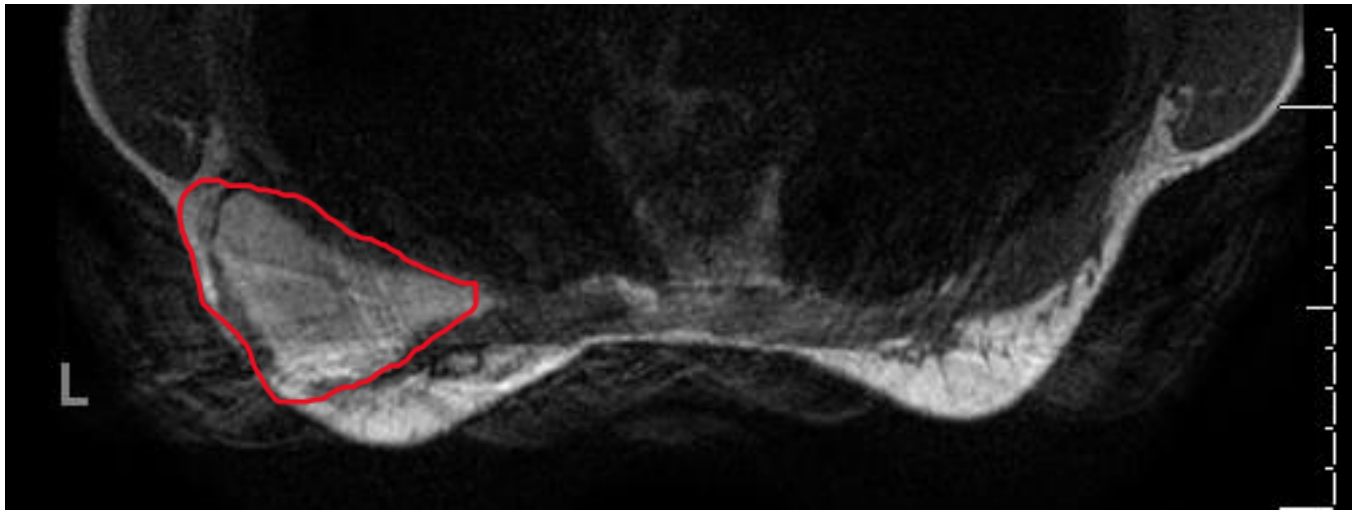






Case examples

Atypical lipomatous tumor



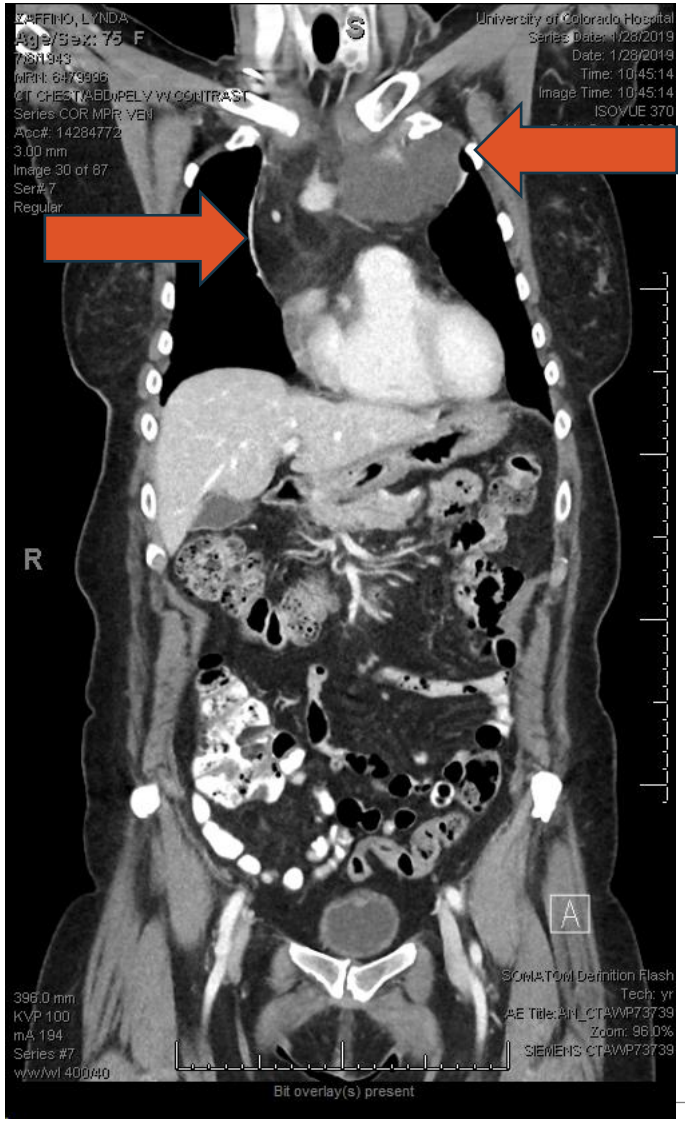
- 48 yo F with long history of multiple recurrent “lipomas” resected from same site in chest wall in 2009, 2014, 2021
- Outside path continued to call “lipoma”
- Recurrent again 9/2022, presented to sarcoma clinic and review of path confirmed atypical lipomatous tumor with MDM2 amplification by FISH
- Oncologic resection 11/8/2022 with reconstruction
- Free of disease as of last imaging 12/2025

Case examples

Well-differentiated liposarcoma

- 75 yo F who presented with shortness of breath
- Diagnosed outside hospital with “dedifferentiated liposarcoma” of mediastinum
- No response to doxorubicin/olaratumab
- Our review of biopsy identified well-differentiated liposarcoma
- Debulking resection 3/1/2019, clinical improvement, MDM2 amplification confirmed well differentiated liposarcoma
- Progression by 5/2020

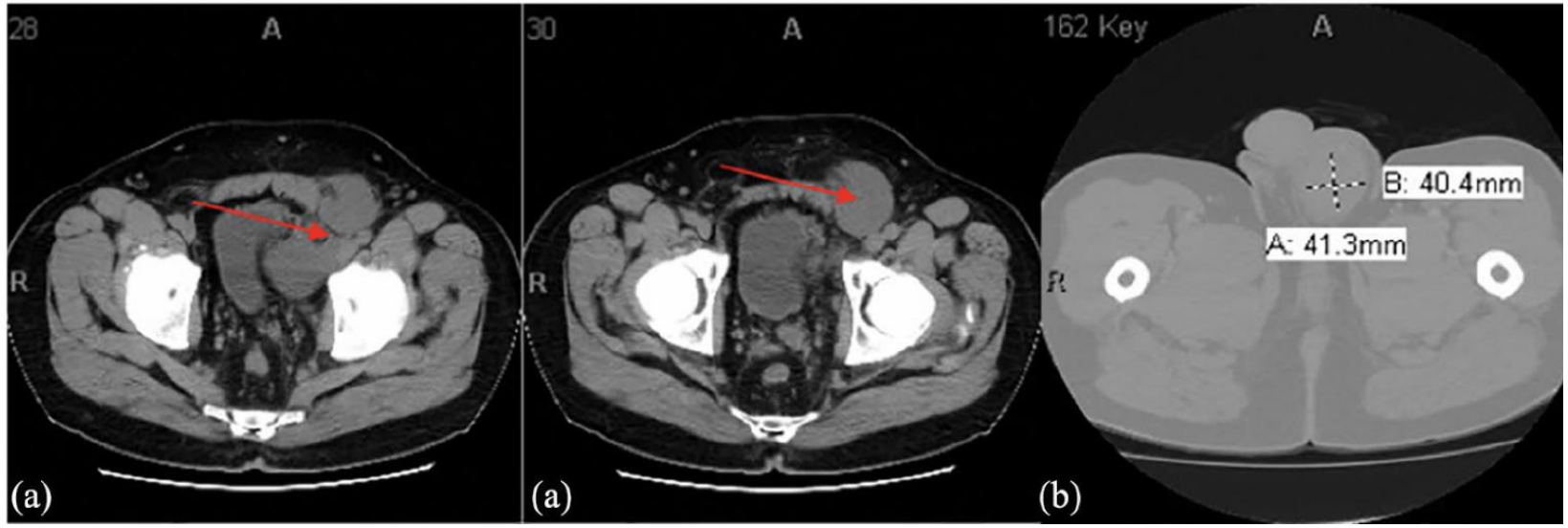
ALT vs well-diff LPS terminology to emphasize risk due to critical structure involvement



Case examples

Dedifferentiated liposarcoma mistaken as a spermatic cord lipoma

- 54 yo M who presented with left-sided inguinal mass, mild discomfort
- Diagnosed with indirect inguinal hernia
- Repaired robotically using mesh at outside community hospital
- Intraoperatively noted a large spermatic cord “lipoma” associated with hematoma
- NOT sent for pathology.

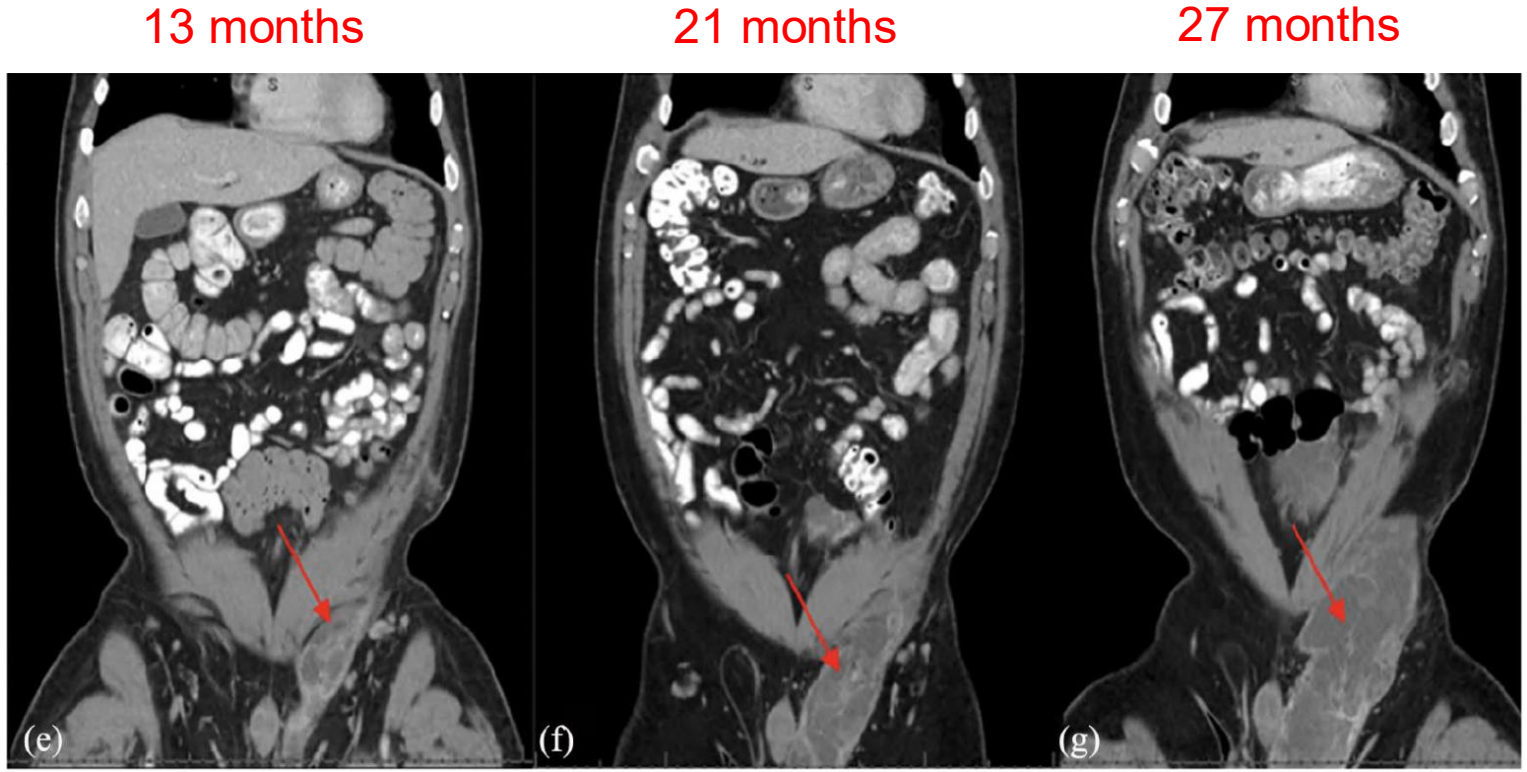


Case examples

Dedifferentiated liposarcoma mistaken as a spermatic cord lipoma

- Recurrent “fluid collections” at site attributed to mesh complications, drained repeatedly, pathology was sent but non-diagnostic.

- 2 additional laparotomies to break up “loculated fluid collections”
- Finally referred to urology at CU 27 months after original surgery, concern for cystic mass
- Dediff liposarcoma…



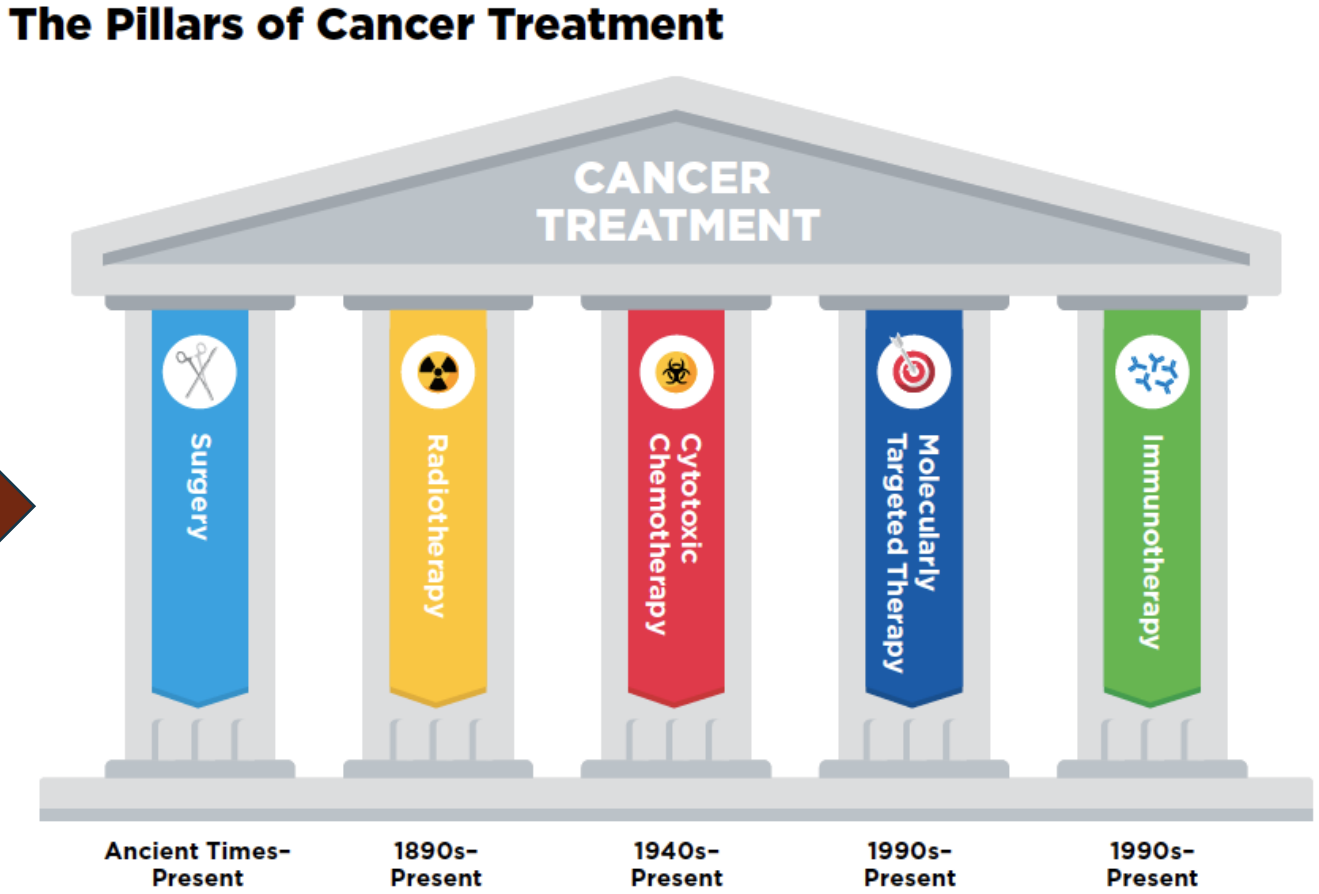
Muir et al, Rare Tumors 2020

Take-home Number 1

- Get the diagnosis right!
- Second opinion for path review is important for treatment decisions and prognosis

A multidisciplinary approach is critical for best outcomes.

- Surgical oncology
- Orthopedic oncology
- Medical oncology
- Radiation oncology
- Musculoskeletal diagnostic/interventional radiology
- Bone/soft tissue pathology
- Molecular pathologists
- Social workers/psychologists

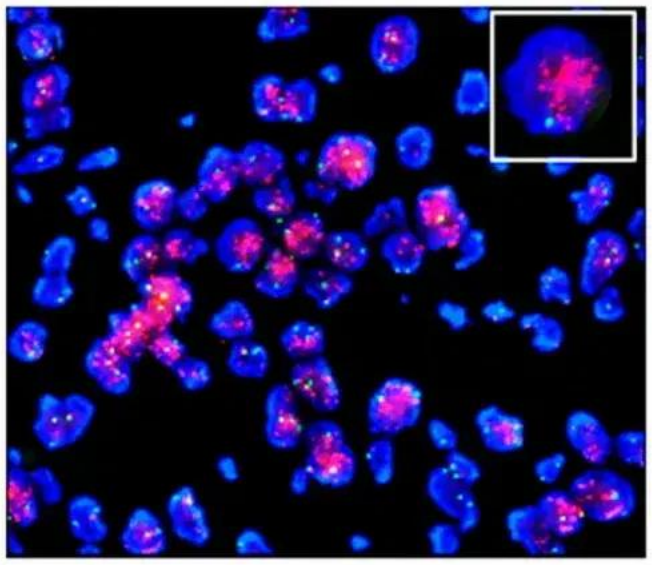


AACR Cancer Progress Report 2023

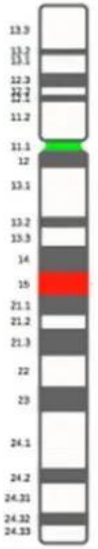
The treatment journey

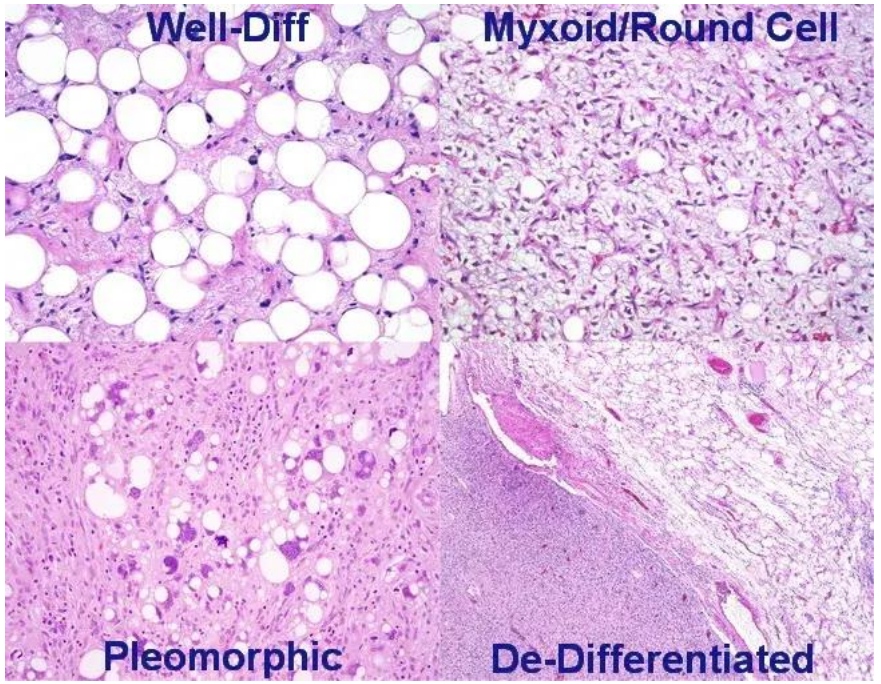
Step 1 – Confirm the diagnosis!!!

- Histologic interpretation by bone/soft tissue pathology
- Molecular testing for MDM2 amplification or DDIT3 fusion by FISH or WGS



Red – MDM2





Liposarcoma, WHO Classification, Web Pathology

The treatment journey

Step 2 – Good imaging and staging

- Myxoid liposarcomas can spread to strange places – need PET or bone scan, MRI total spine, whole body MRI in some centers

Step 3 – Evaluate for resectability

- Surgery remains the gold standard for cure
- In the retroperitoneum this may involve complicated resections of involved organs – try to remove "en bloc" (all in one piece)
- Frequently require removal of kidney, spleen, portions of bowel, vascular reconstructions…

Neoadjuvant treatment

Step 4 – Role for treatment prior to surgery to shrink the tumor?

- Depends on location and liposarcoma type
- Multidisciplinary discussion is critical
- Personalized decision making/recommendations for the individual patient and case
- Practice can vary across centers
- Typically only considered if tumor greater than 5 cm

Neoadjuvant treatment

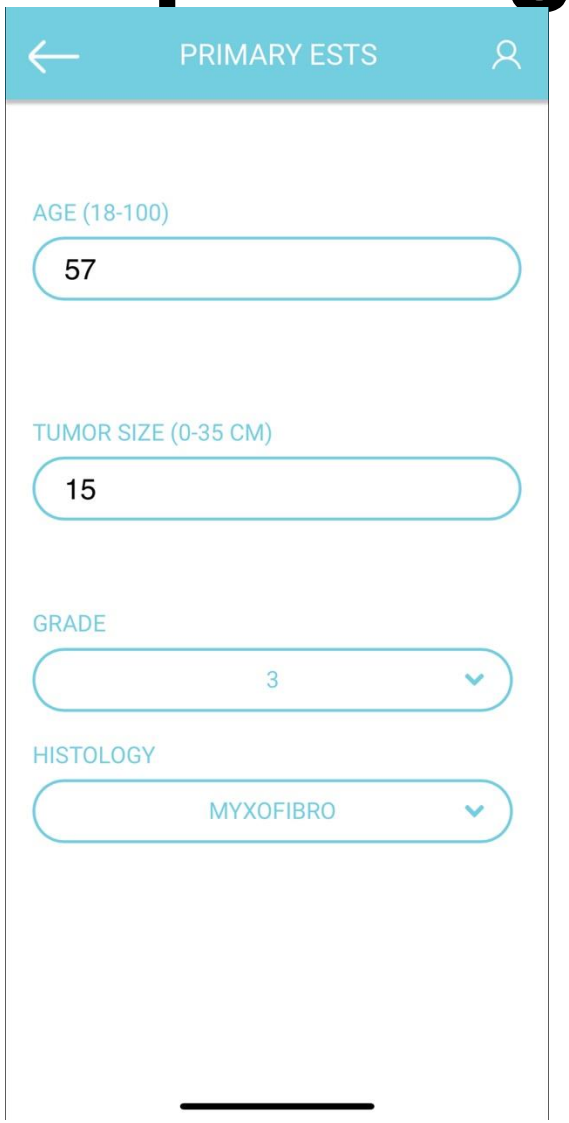
Step 4 – Role for treatment prior to surgery to shrink the tumor?

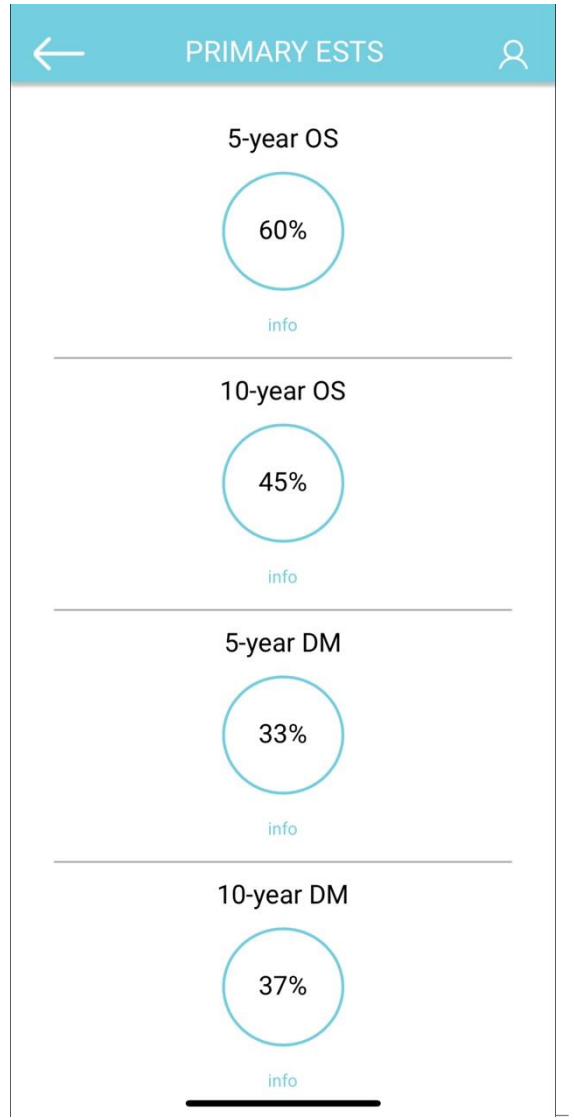
Location	Well-diff LPS / ALT	Dediff LPS	Myxoid LPS (low grade)	Myxoid LPS (high grade)	Pleomorphic LPS
Extremity or trunk	Surgery only and preserve critical structures (minimal response to chemo or radiation)	Pre-op radiation, consider chemotherapy or immunotherapy	Surgery only, consider pre-op radiation/chemo if borderline resectable or margins likely to be close	Pre-op radiation, consider chemotherapy	Pre-op radiation, consider chemotherapy
Retroperitoneum		Radiation and chemo are controversial!	Very rare	Very rare	Very rare

Neoadjuvant treatment paradigms

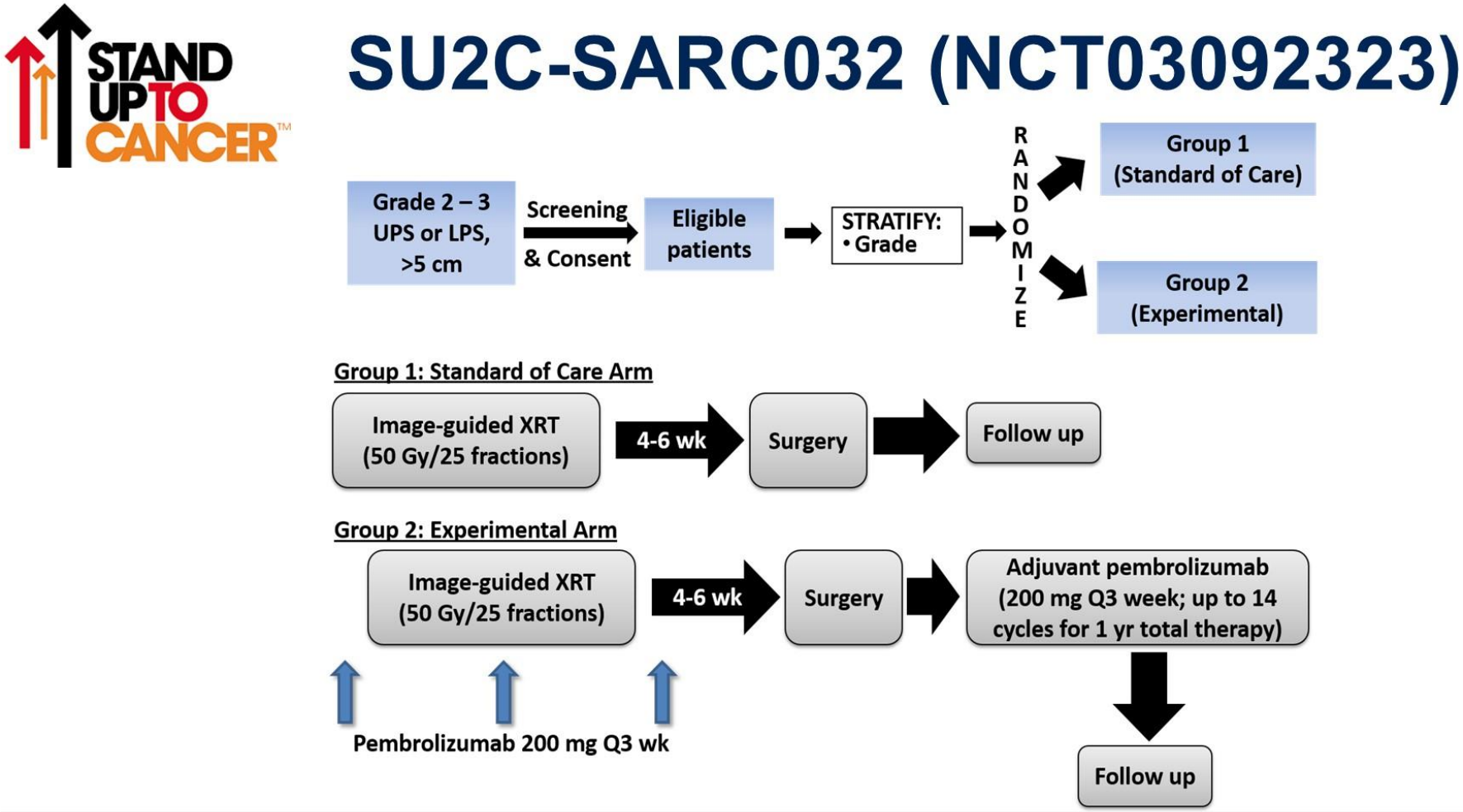
Extremity/trunk liposarcomas

- Radiation therapy standard practice to improve local control for high grade tumors > 5 cm (Stage III)
- Systemic chemotherapy options:
  - Estimate survival risk (Sarculator)
  - **Doxorubicin/ifosfamide** (the winner for most STS with predicted low overall survival)
  - Low responses for dediff LPS and pleomorphic, better for myxoid/round cell
  - **Trabectedin** (myxoid/round cell)





SU2C-SARC32 - pembrolizumab

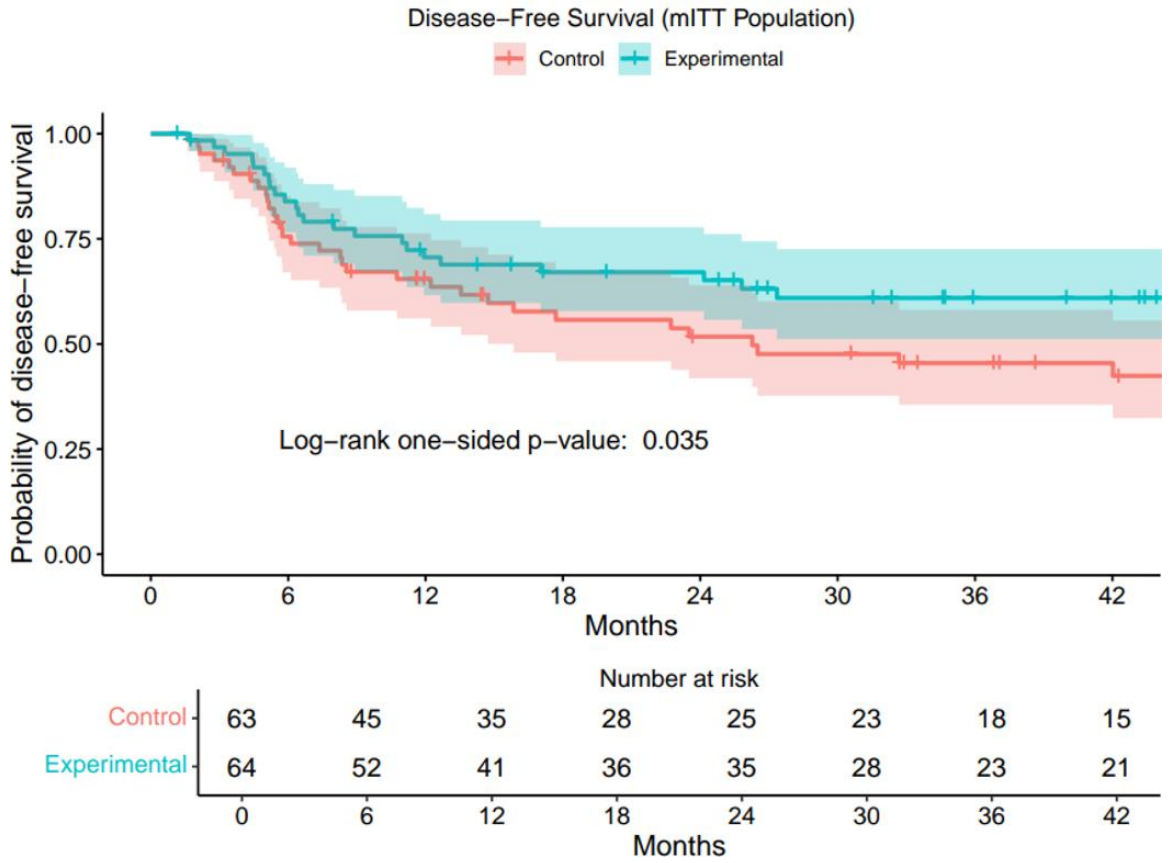


Kirsch et al, ASCO 2024

SU2C-SARC32 -

Characteristic	Control, n = 63	Experimental, n = 64
Grade		
Grade 2	20 (32%)	22 (34%)
Grade 3	43 (68%)	42 (66%)
Sarcoma Histologic Subtype at Initial Diagnosis		
Dedifferentiated Liposarcoma	4 (6%)	4 (6%)
Pleomorphic Liposarcoma	5 (8%)	0 (0%)
Myxofibrosarcoma	6 (10%)	7 (11%)
Undifferentiated Pleomorphic Sarcoma	48 (76%)	53 (83%)
Tumour Location		
Lower limb	38 (60%)	41 (64%)
Lower limb girdle	6 (10%)	3 (5%)
Upper limb	9 (14%)	10 (16%)
Upper limb girdle	10 (16%)	10 (16%)
Tumor Size (cm)		
Median (IQR)	10 (7, 13.4)	11 (7.9, 14)
Not available	0	1
RT		
Any Hypofractionated RT	2 (3%)	1 (2%)
Conventionally Fractionated RT	61 (97%)	63 (98%)

A



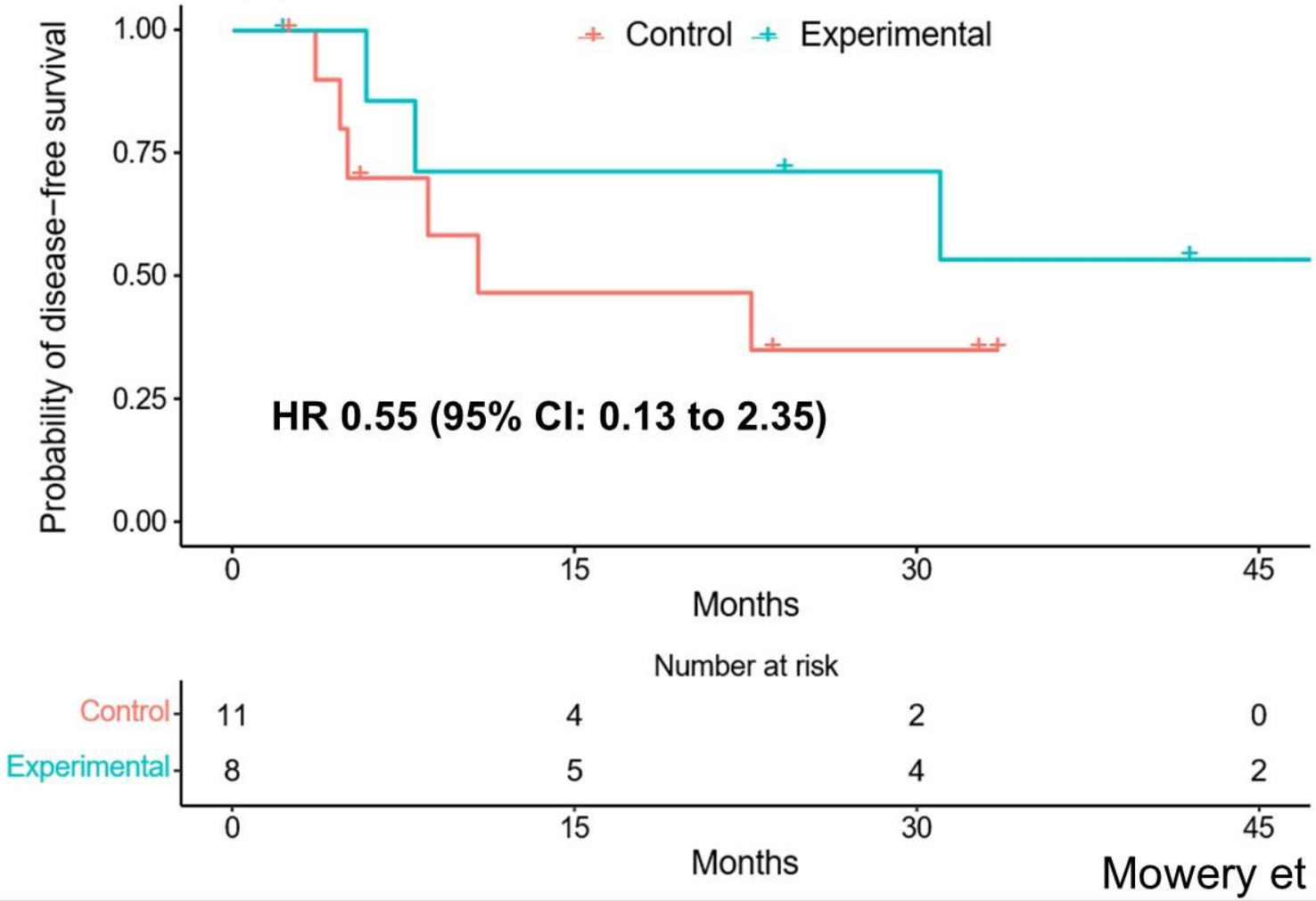
Two-year DFS increased by 15% with addition of pembrolizumab: 52% (90% CI, 42 to 64) and 67% (90% CI, 58 to 78) for control and experimental groups, respectively.

Trends towards greatest benefit in grade 3 tumors and distant DFS

Modified from Mowery et al, Lancet 2024

DFS Benefit from Adding Pembrolizumab to RT + Surgery in Patients with LPS

Evaluable Patients



Mowery et al, *Under Review*

PRESENTED BY: David Kirsch, MD, PhD

Neoadjuvant treatment

Retroperitoneal liposarcomas

- Historically treated with surgery alone
- **STRASS I trial** – all retroperitoneal sarcomas - randomized patients to preoperative radiation or surgery alone
  - Overall no significant benefits to local control or overall survival with radiation
  - However, subgroups suggested possible benefit with local control of liposarcomas (especially well-differentiated liposarcomas)
- Chemotherapy with doxorubicin/ifosfamide historically has not improved long term survival, but occasional responses which may help surgical resection
- **STRASS 2 trial** – investigating use of chemotherapy before surgery compared to surgery alone (more tomorrow!)

Bonvalot et al, Lancet Oncol 2020

Post-surgery treatment journey

Step 5 – Follow up after the tumor resection

- Observation – scans every 3-6 months
- Rates of recurrence vary considerably (Sarculator can help some –)
  - ALT – 10-30% local recurrence
  - Well-diff LPS – 40-60% local recurrence, with risk of dedifferentiation about 15%
  - Dedifferentiated LPS – 20-30% in extremity, 40-50% in retroperitoneal disease. Distant metastatic rates 15-30%
- We need better therapies for adjuvant treatment for high risk patients!

Menon & Kaur, StatPearls 2026

Treatment options for recurrent/unresectable disease

Step 6 – Recurrent disease – now what?

Option 1 - Observe – particularly with well-differentiated RP disease, slow rate of growth, small volume, asymptomatic

Option 2 – Proceed with **re-resection** - historically the main approach to recurrent disease – but challenges with multiple repeated surgeries.

- Generally avoided with a short disease-free interval after prior surgery.

Option 3 – Systemic therapy

- Consider systemic chemotherapy to get shrinkage/control to get to surgery.
- Allows for assessment of activity for high risk patients that may choose something after surgery
- Not the greatest options for long-term control. Not great for well-differentiated disease.

Treatment options for recurrent/unresectable disease

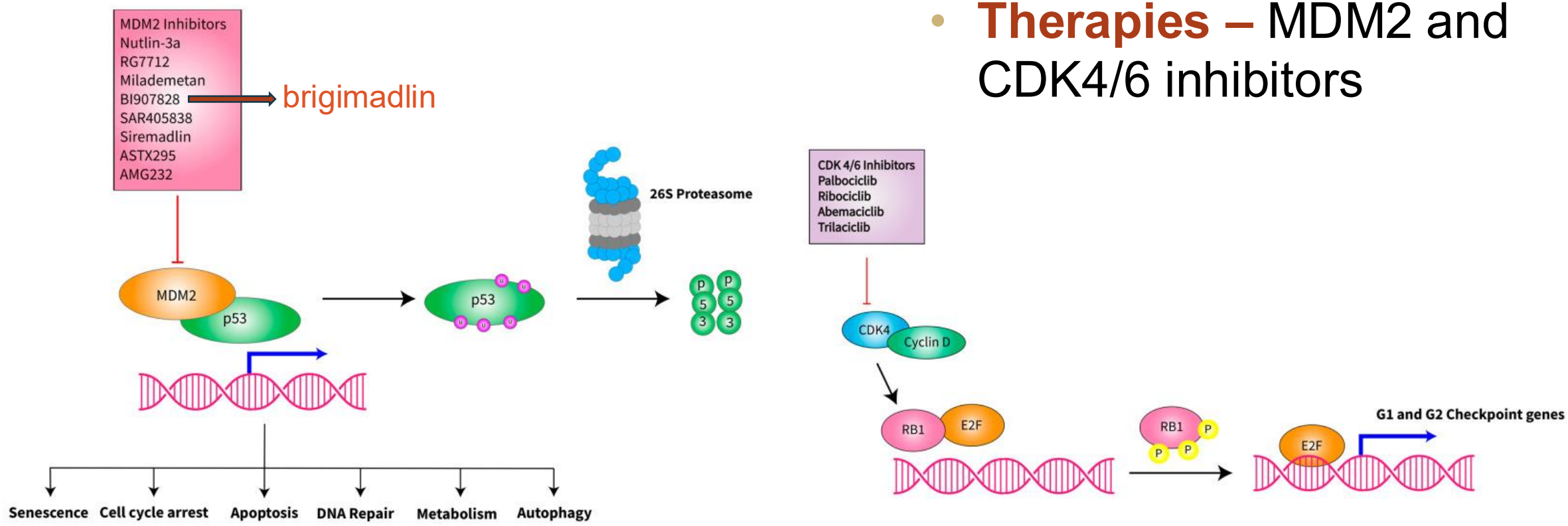
Systemic therapy options

- Approved chemotherapy for dedifferentiated liposarcoma
  - **Doxorubicin** (response rate 8.6%, median PFS 7.2 months)
  - **Gemcitabine/docetaxel** (response rate 9.7%, mPFS 9.2 months)
  - **Trabectedin** (response rate < 10%, mPFS 2.2 months)
  - **Eribulin** (response rate 4%, mPFS 2.6 months)
- Immunotherapy – (checkpoint inhibitors, pembrolizumab, nivolumab)
  - Only about a 10% response rate and tends not to be durable

Schoffski et al, Clin Cancer Res 2026
Thirasastr et al, Cancer Med 2023
Demetri et al, JCO 2016
Osgood et al, Clin Canc Res 2017
Tawbin et al, Lancet Oncol 2019

Targeted therapies for well-diff/dediff liposarcomas

- **Targets –** amplifications of chromosome region 12q13-15, contains *MDM2* and *CDK4* (>90%, or p53 mutant)



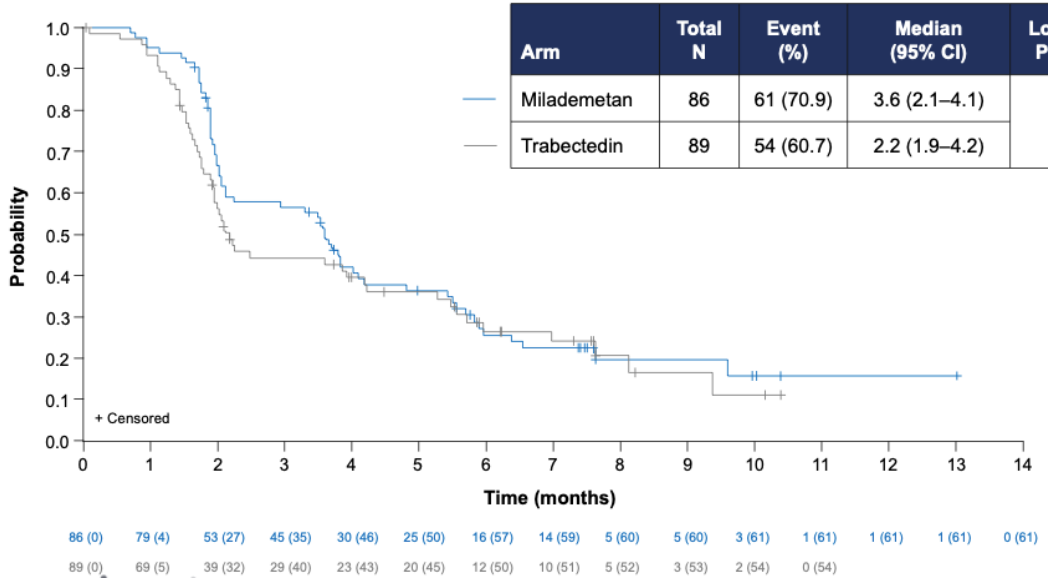
- **Therapies –** MDM2 and CDK4/6 inhibitors

Zhou et al, Int J Mol Sci 2023

Targeted therapies for well-diff/dediff liposarcomas

- **MDM2** – the not so good – toxicities and chemo outcomes

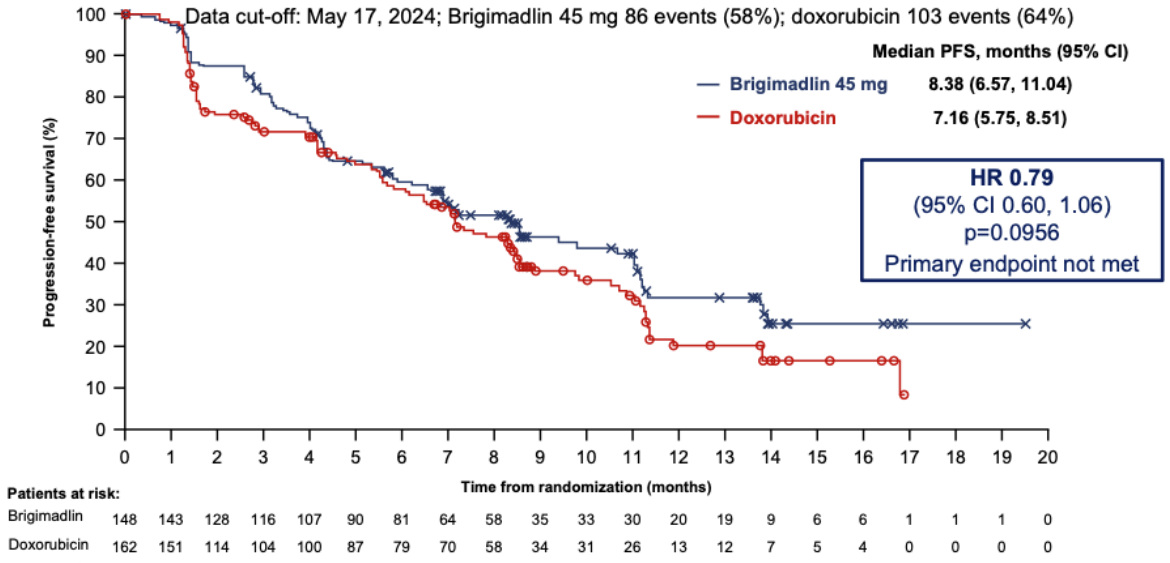
Progression-free survival (BICR)



Arm	Total N	Event (%)	Median (95% CI)	Log-rank P-value	HR (95% CI)
Milademetan	86	61 (70.9)	3.6 (2.1–4.1)	0.53	0.89 (0.61–1.29)
Trabectedin	89	54 (60.7)	2.2 (1.9–4.2)		

Take-home – at least brigimadlin is an active drug, but over-ambitious study design?

PRIMARY ENDPOINT: PFS BY BLINDED INDEPENDENT CENTRAL REVIEW

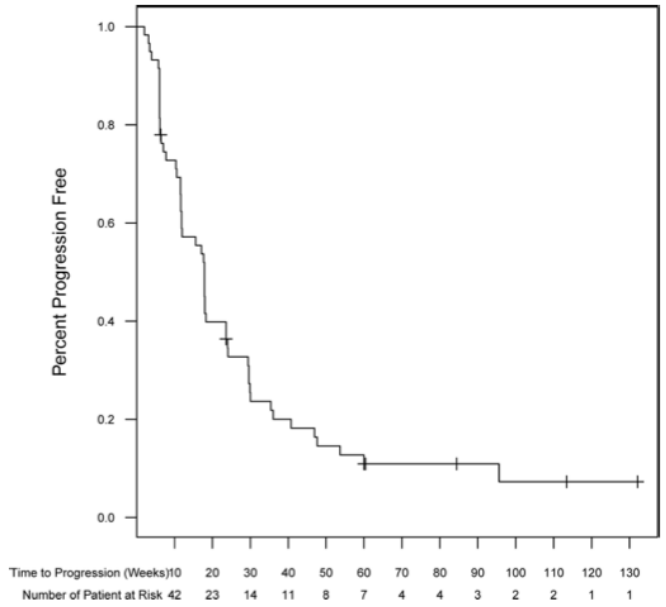


Sanfilippo et al, CTOS 2023
Schöffski et al, CTOS 2024

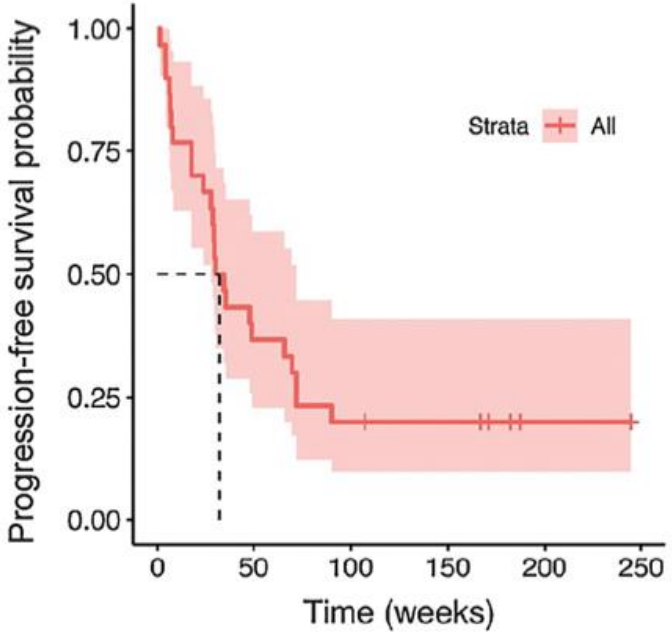
Targeted therapies for well-diff/dediff liposarcomas

- **CDK4(6) –**

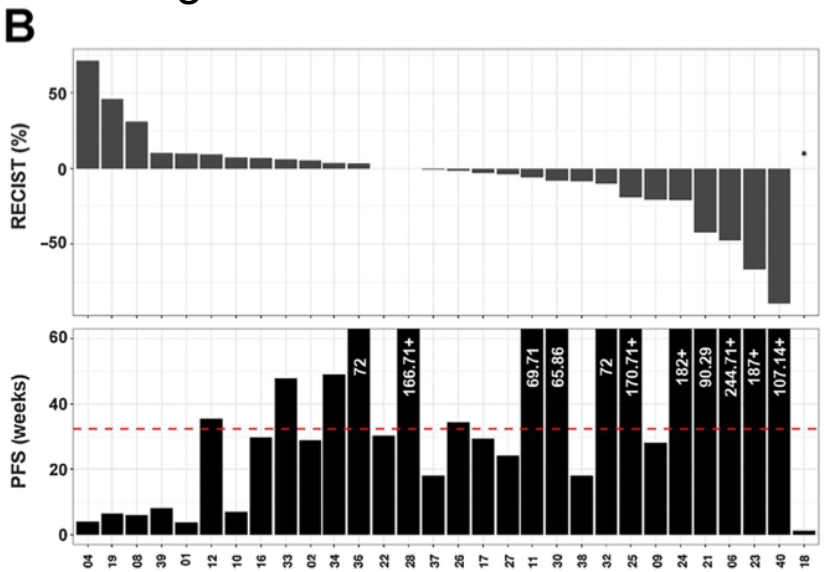
Palbociclib – mPFS 17.9 weeks – some long-term responders



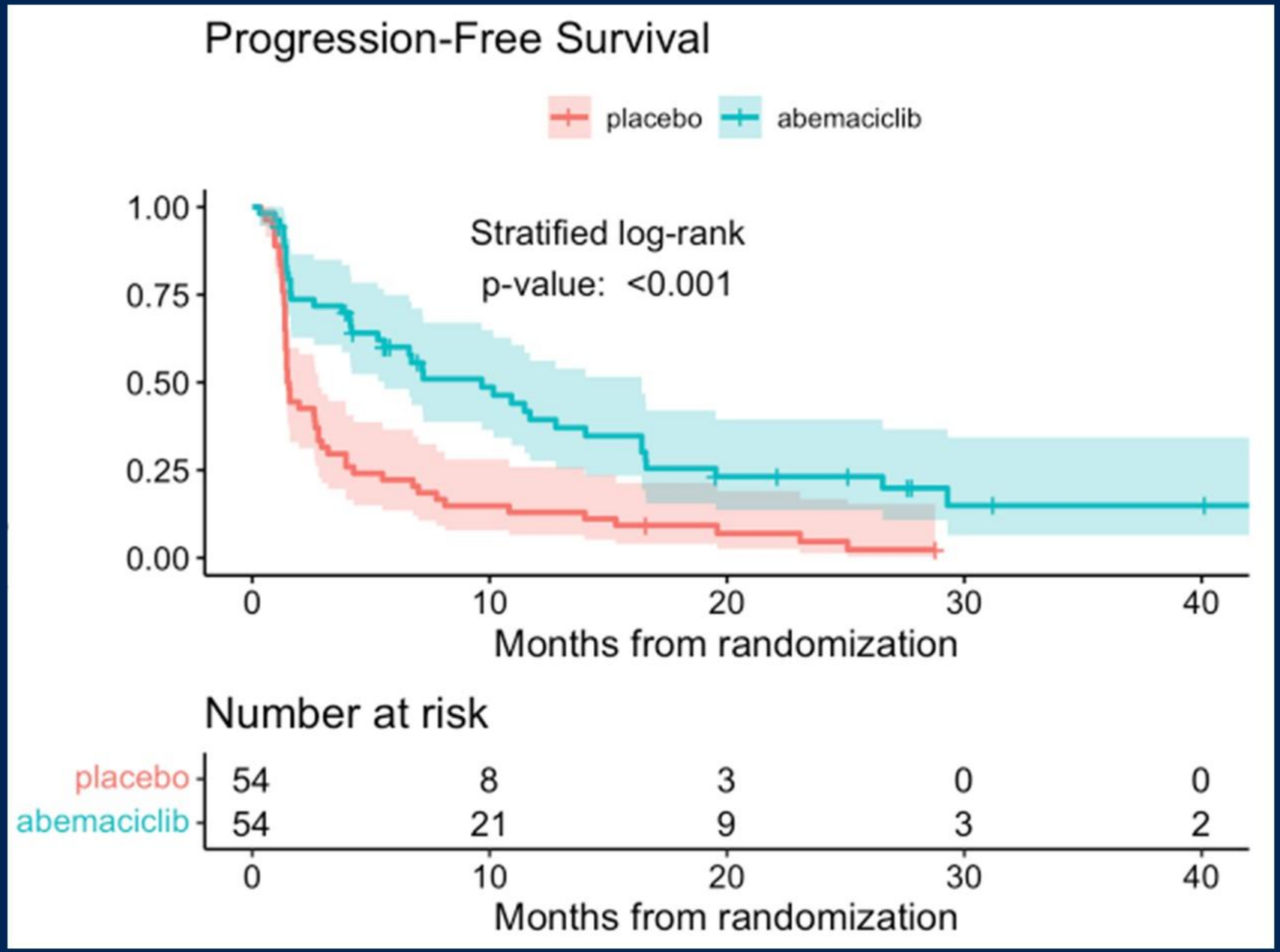
Abemaciclib – mPFS 33 weeks



6 / 30 patients had long term stable disease for two years or longer



Dickson et al, JAMA Oncol 2016
Gleason et al, Clin Cancer Rese, 2024



Primary endpoint

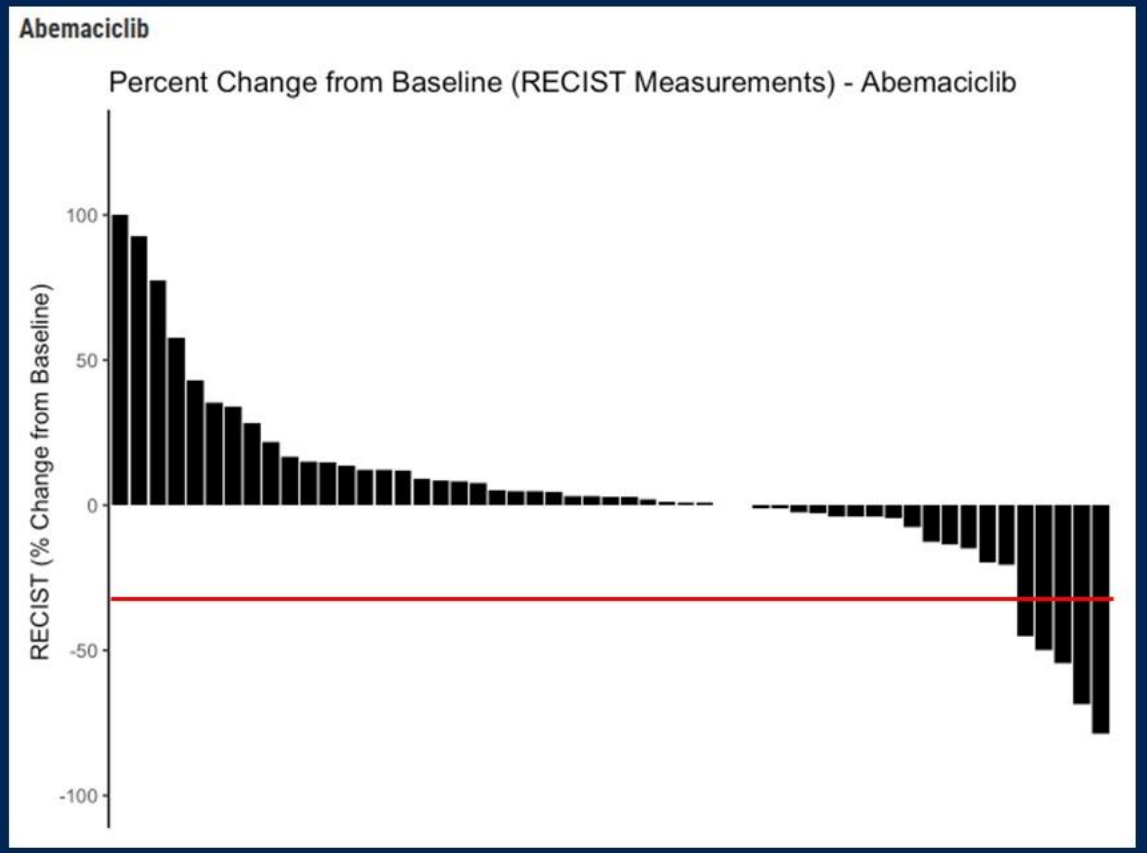
Median PFS
- abemaciclib: 9.7 months
- placebo: 1.5 months

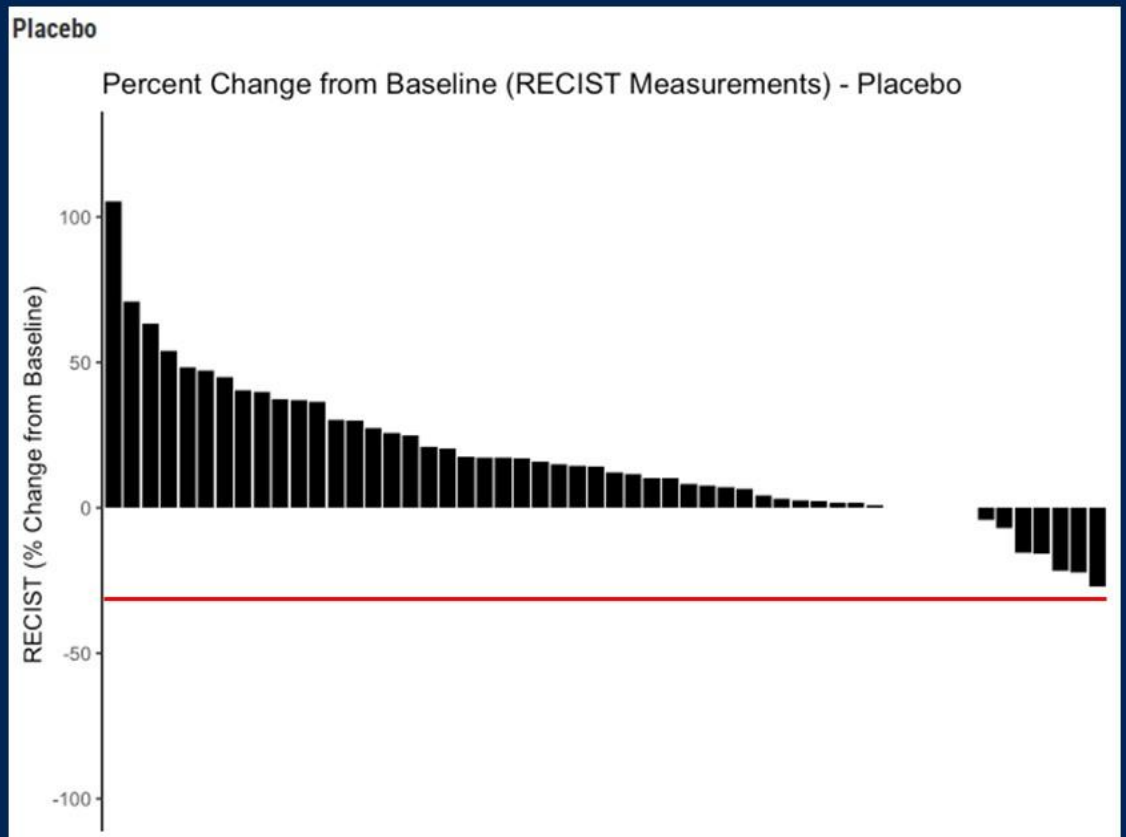
Hazard ratio 0.38
(90% CI: 0.25-0.59, p <0.001)

6-month PFS
- abemaciclib: 60%
- placebo: 22%

12-month PFS
- abemaciclib: 39%
- placebo: 13%

Response Rate





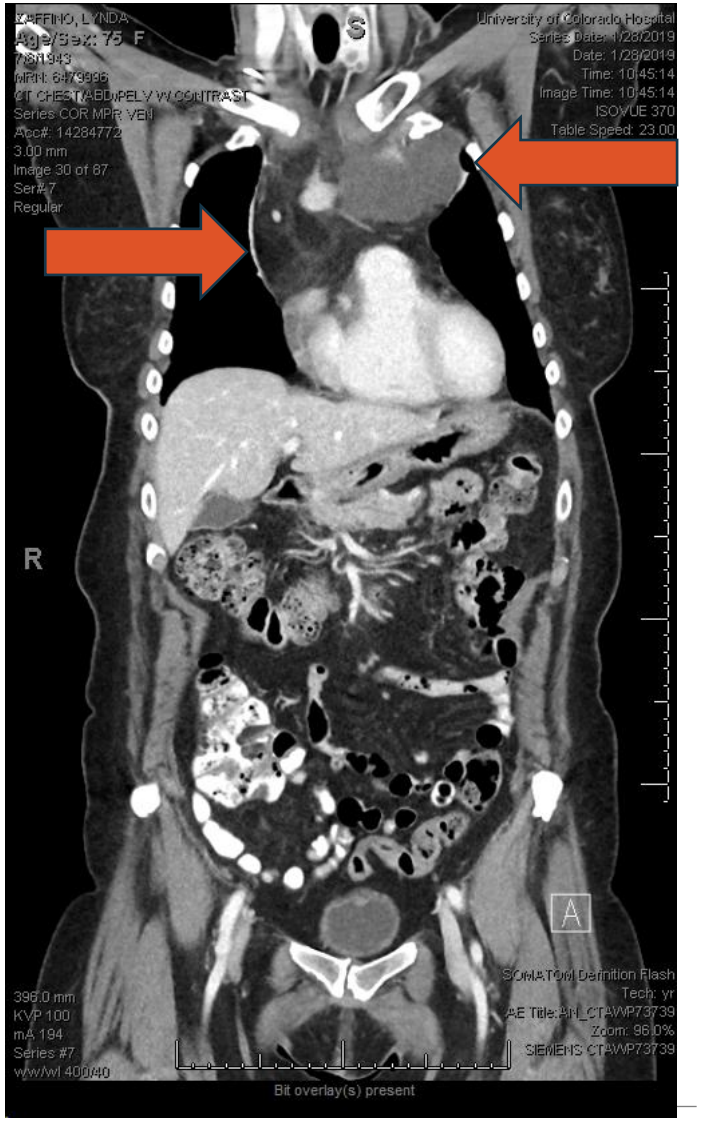
Abemaciclib ORR 9%

Placebo ORR = 0

Back to one of our patients…

Well-differentiated liposarcoma

- 75 yo F with mediastinal well-differentiated liposarcoma
- Debulking resection 3/1/2019, clinical improvement
- Progression by 5/2020
- Treated with definitive radiation therapy 7/2020
- Progression October 2020
- Initiated on **abemaciclib** 11/21/2020 with arrest of growth!
- Has continued on very low dose therapy 50 mg twice daily 4 weeks on, 2 weeks off
- Continues with stable disease as of March 2026



Areas for research and improvement

AKA My wish list!

- Better therapies for pre- and post-surgery –abemaciclib in trials in the neoadjuvant and adjuvant setting?
  - Growth arrest is a good thing if you have minimal residual tumor cells!
- Understand biology of resistance to chemo or targeted therapies and develop new drugs for those escape mechanisms
- How else can we target liposarcoma cells? New targets? Antibody-drug conjugates? (trojan horse drugs)
- How can we better use immunotherapy? Checkpoint inhibitors in combination with chemotherapy? Better biomarkers to find the magic 10% patients who will truly benefit?
- We need more treatment options for myxoid/round cell liposarcomas and pleomorphic liposarcomas – hope for T cell therapies for myxoid/round cell but still minority of patients with the correct tissue type. Checkpoint inhibitors ineffective.

Summary and Take-Homes

- Pathology review is critical in the early stage of diagnosis, liposarcomas can hide behind more common benign entities, or mask as different sarcoma types when they reprogram themselves
- Optimal management of liposarcomas requires an experienced multidisciplinary team, given the variability of the biology and individual patient scenario
- Surgery remains the mainstay of treatment and best hope for durable disease-free survival
- CDK4/6 blockade with abemaciclib is the most promising systemic therapy, but doesn't work for all patients and can be limited by development of resistance
- Chemotherapy still has a role, especially to try to get patients to surgery, but leaves a lot to be desired as a longer term management strategy
- Exciting upcoming studies give hope for targeting LPS differently!

Acknowledgements

Wilky Lab (*Past* and Present!):

Cristiam Moreno Tellez, MD
Lindsey Kemp, BS
M. Jane Underdown, MD (Peds Heme-Onc, Utah)
Nick Therrien, MS (PhD candidate, Mayo Clinic)
Maureen Mida, MS
Sumra Chaudhry, BS (Post-Bacc Scholar)
Jeff Rytlewski, MD (Heme-Onc fellow)
Qierra Brockman, PhD
Macy Falk, BS

Davila Lab:

Eduardo Davila, PhD

Families of Cheryl Bennett and Ward McNeilly
Sarcoma Philanthropic Research Funding
Clinical Trial patients and families

Cancer League of Colorado

American Cancer Society

SYLVESTER Comprehensive Cancer Center, University of Miami Health System

nanoString

Sarcoma Foundation of America — finding the cure in our time

University of Colorado Cancer Center

Sarcoma Program
University of Colorado Anschutz Medical Campus


University of Colorado Anschutz Medical Campus
THANK YOU
Email: breelyn.wilky@CUAnschutz.edu. X: @breelynwilkyMD

LIPOSARCOMA SUPPORT NETWORK

Thank you to our sponsors for supporting our mission to present high-quality education, engagement & support to the liposarcoma community!

ADI bioscience

IOVANCE BIOTHERAPEUTICS

Lamassu ACCELERATING HOPE AND HEALING

STORM THERAPEUTICS

VANDERBILT-INGRAM CANCER CENTER

Cancer UT MD Anderson

SYLVESTER COMPREHENSIVE CANCER CENTER UNIVERSITY OF MIAMI HEALTH SYSTEM

The James
THE OHIO STATE UNIVERSITY COMPREHENSIVE CANCER CENTER