

Sarcoma Immunotherapy

SPAEN 2018

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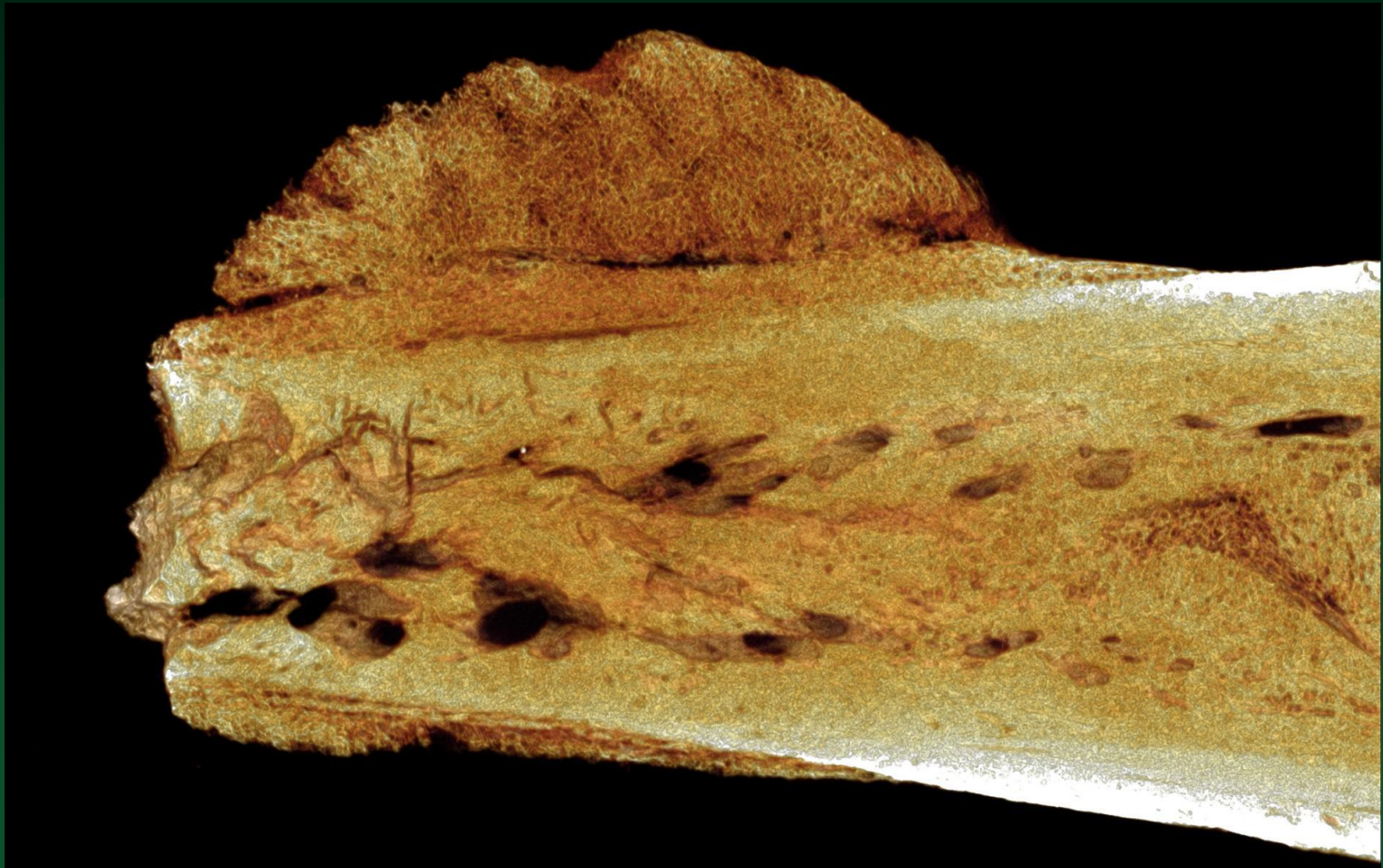


Disclosures

- **Research funding – Blueprint, Plexxicon, Lilly**
- **Advisory Boards – Janssen, Lilly, Novartis, Deciphera, Blueprint, Plexxicon**
- **Off-label uses of non-FDA approved drugs will be discussed**

First Cancer (Osteosarcoma)

~1.7 million years ago



Randolph-Quinney, et al. SAJS, 2016

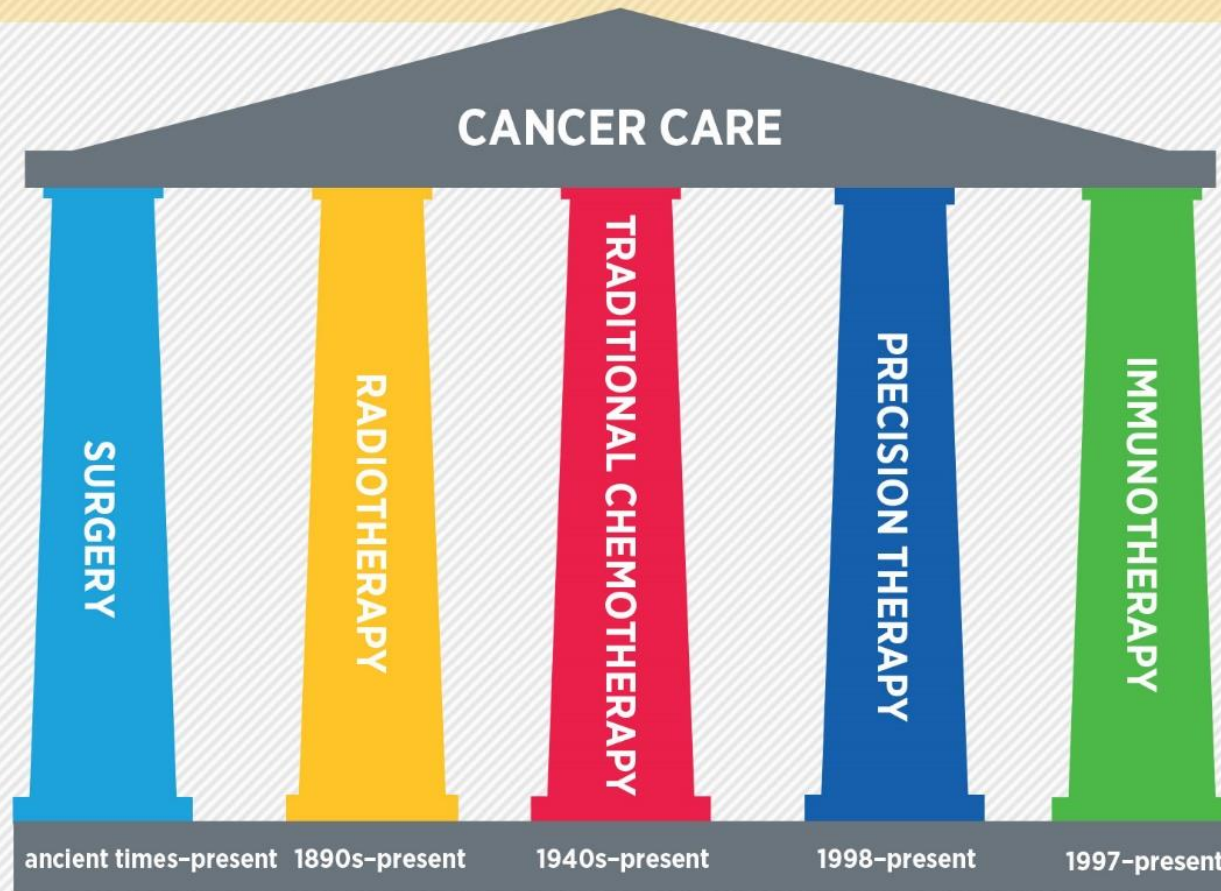
Current Classification of Sarcomas

- **Vascular STSs**
 - Angiosarcoma
 - Hemangiosarcoma
 - Lymphangiosarcoma
 - Hemangioendothelioma
 - Hemangiopericytoma
 - Kaposi's Sarcoma
- **Neural STSs**
 - Malignant Peripheral Nerve Sheath Tumor
 - Malignant Paraganglioma
 - Neuroblastoma, Neuroepithelioma
 - Granular Cell Tumor
- **Adipose STSs**
 - ALT
 - Myxoid/Round cell Liposarcoma
 - Dedifferentiated Liposarcoma
- **Pleomorphic STSs**
 - Lipo, MFH
- **Neuromuscular STS**
 - GI Stromal Tumor
- **Unclassified**
- **Smooth Muscle STSs**
 - GI, GU, Cutaneous, Vascular
- **Skeletal Muscle STSs**
 - ARMS, ERMS, Pleomorphic RMS
- **Fibrous STSs**
 - Fibrosarcoma (myxo-, myo-)
 - Fibromyxoid Sarcomas
 - Desmoid Tumor
 - Dermatofibrosarcoma
 - Inflammatory myofibroblastic tumor
- **Unknown Tissue**
 - Synovial Sarcoma
 - ASPS
 - Epithelioid Sarcoma
- **Bone Sarcomas**
 - Osteosarcoma (+ variants)
 - Chondrosarcoma (+ variants)
 - Giant Cell Tumor of Bone
 - Ewing's Sarcoma Family of Tumors
- **Extraskelatal Bone Sarcomas**
 - Osteosarcoma
 - Primitive Neuroectodermal Tumor
 - Chondrosarcoma

Therapeutic Paradigms

FIGURE 4

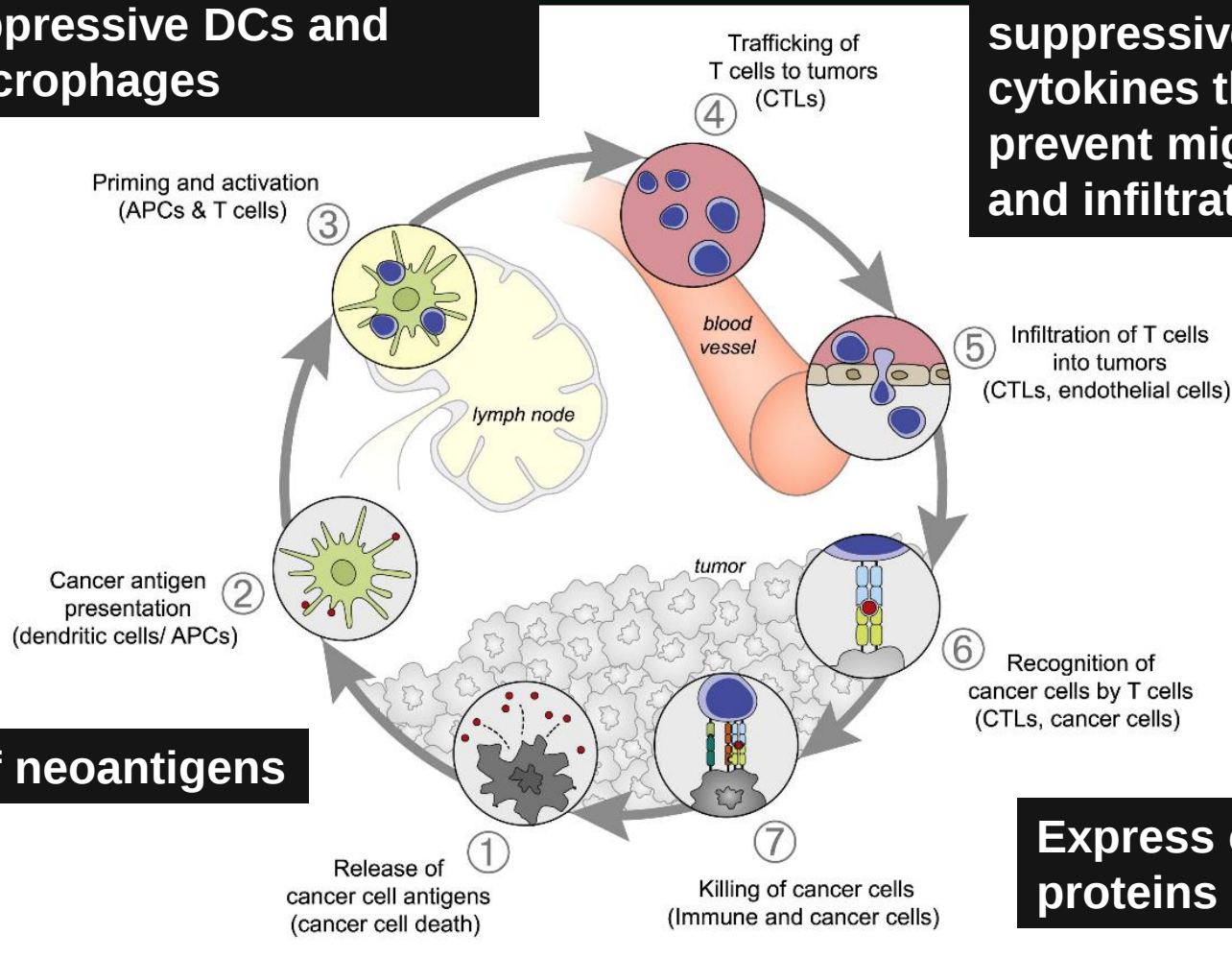
MORE OPTIONS FOR CANCER CARE



Anti-tumor Immunity

Promote immature, suppressive DCs and macrophages

Produce suppressive cytokines that prevent migration and infiltration



Landscape of Immunotherapy in Sarcoma

Past

- Vaccines (antigens, dendritic cell, combination), cytokine therapies (interleukins/mifamurtide)

Present

- NY-ESO-1 directed therapies
- PD-1, CTLA-4 checkpoint inhibitors and combinations
- Biomarkers and resistance mechanisms

Future

- CAR T cells – new targets
- Oncolytic viruses
- Hundreds of novel immunomodulating drugs
- Precision immunotherapy (immunogram?)
- Combinations with other IO and other agents

Wilky and Goldberg et al, Discov Med 2017, Burgess et al, Curr Oncol Rep 2015

Open Label Non-Randomized Multi-Cohort Pilot Study of Genetically Engineered NY-ESO-1^{c259T} in HLA-A2⁺ Patients with Synovial Sarcoma (NCT01343043)

Crystal Mackall¹, William Tap², John Glod³, Mihaela Druta⁴, Warren A. Chow⁵, Dejka Araujo⁶, Stephan Grupp⁷, Brian Van Tine⁸, Karen Chagin⁹, Erin Van Winkle⁹, Gabor Kari⁹, Trupti Trivedi⁹, Elliot Norry⁹, Tom Holdich⁹, Lini Pandite⁹, Rafael Amado⁹, Sandra P. D'Angelo²

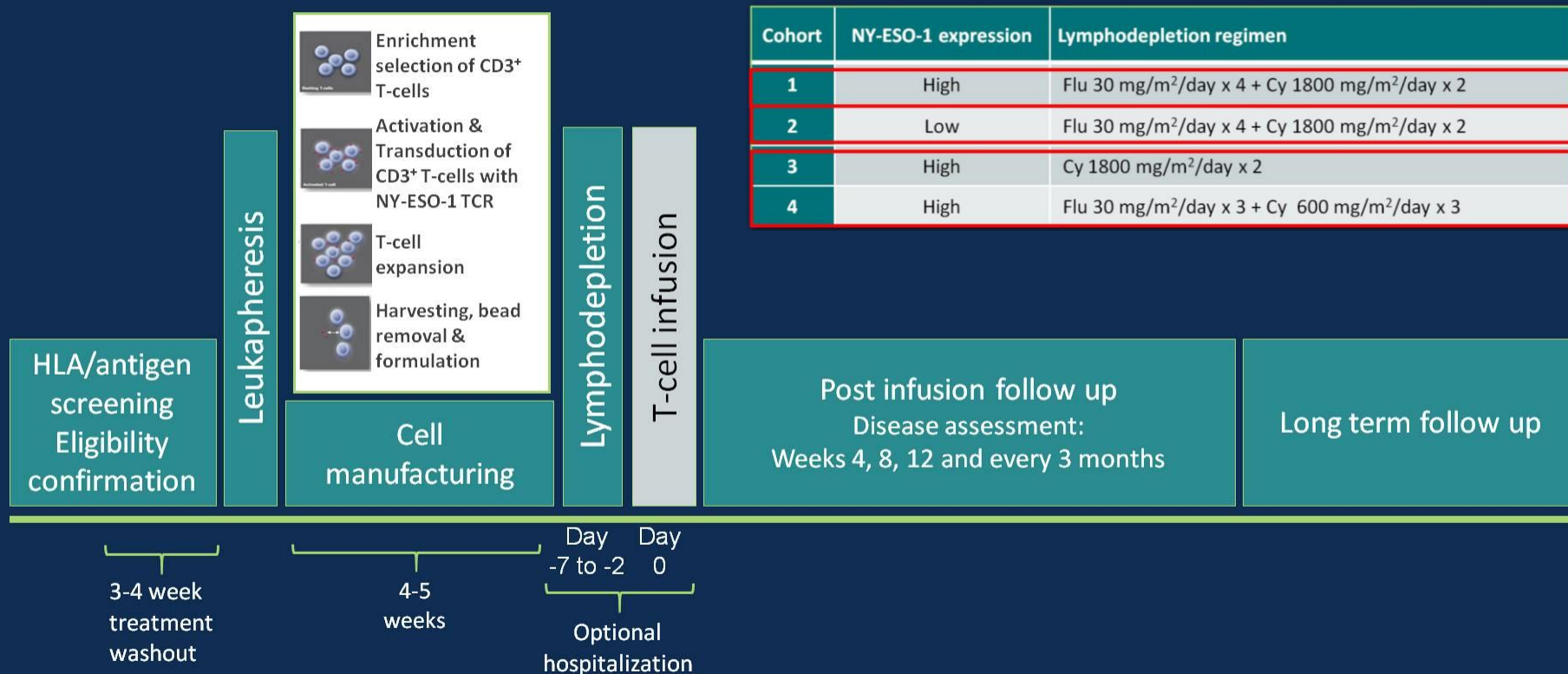
1. Stanford 2.MSKCC 3.NIH 4.Moffit 5.CoH 6.MDACC 7. UPENN 8. WUSTL 9. Adaptimmune

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Overview of Study Design



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Response Summary

	Cohort 1 Hi NY-ESO-1 Hi Flu/Cy N=12	Cohort 2 Lo NY-ESO-1 Hi Flu/Cy N=5	Cohort 3 Hi NY-ESO-1 Cy N=5	Cohort 4 Hi NY-ESO-1 Mod Flu/Cy N=6
Best overall response: N (%)				
CR	1 (8)	0 (0)	0 (0)	0 (0)
PR	5 (42)	2 (40)	1 (20)	3 (50)
SD	6 (50)	1 (20)	4 (80)	2 (33)
PD	0 (0)	1 (20)	0 (0)	1 (17)
Not assessed	0 (0)	1 (20)	0 (0)	0 (0)
ORR: Confirmed, CR + PR: N (%)	6 (50)	2 (40)	1 (20)	3 (50)
Median PFS: weeks (range)	15 (8, 38)	12 (03- 14)	12 (8, 38)	NE
Median response duration: wks (range)	30.9 (13, 72)	7.5 (6-9)	21--	NE

ORR – 12/28 patients, 43%

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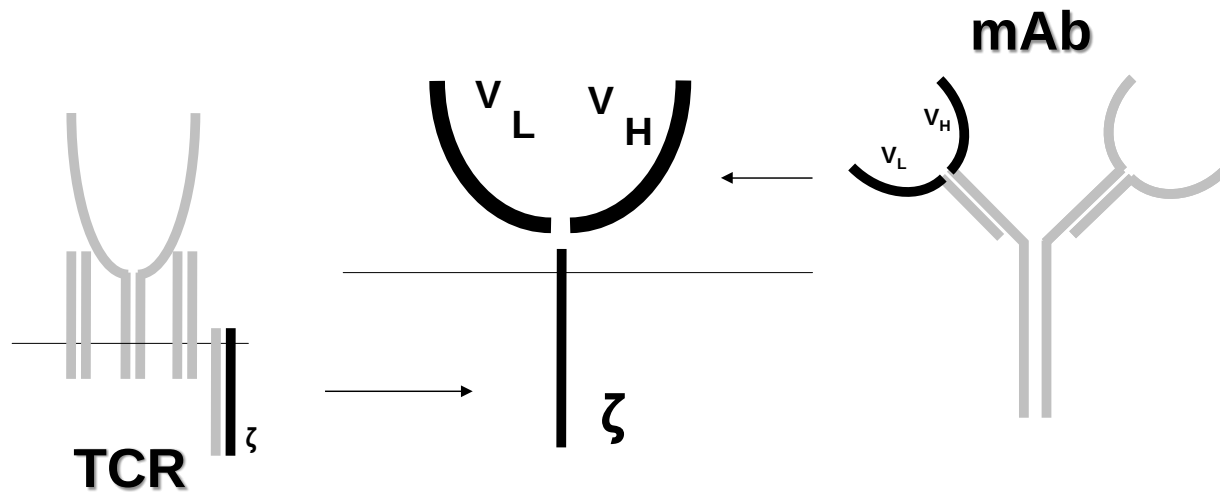
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The CAR

Chimeric Antigen Receptor

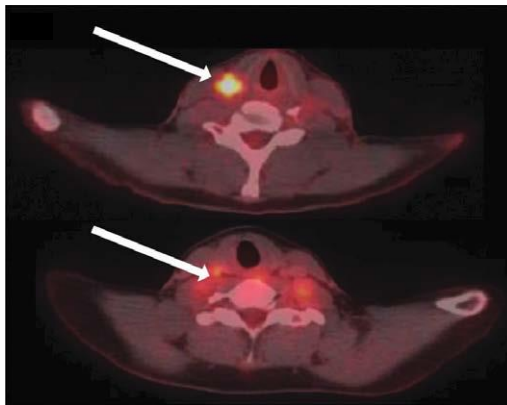


TCR= T-cell receptor complex
mAb= Monoclonal antibody
CAR= Chimeric antigen receptor

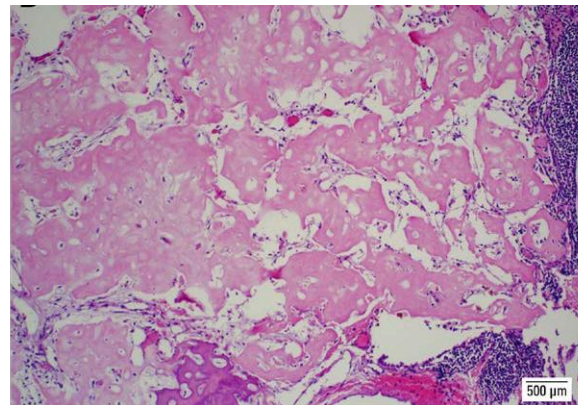
Eshhar et al PNAS '93

HEROS: HER2 CAR T cells for OSarcoma

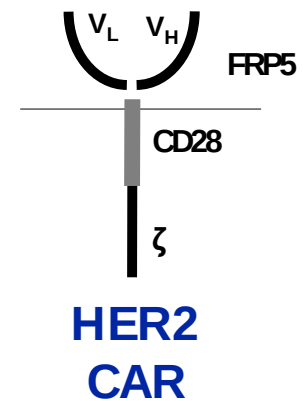
- Phase 1 dose-escalation study ($1 \times 10^4 / \text{m}^2$ - $1 \times 10^8 / \text{m}^2$)
- 19 subjects treated; NO DLTs
- 1 PR, 3 SD



Patient with PR



> 90% necrosis post-infusion



Drug(s)	Target	Indication
Ipilimumab	CTLA4	• Unresectable metastatic melanoma • Adjuvant Stage III melanoma
Pembrolizumab	PD-1	• Advanced/unresectable melanoma • First line and Metastatic NSCLC (PDL1) • Recurrent squamous cell carcinoma of head and neck • MSI high, all solid tumors • Urothelial carcinoma • Hodgkin lymphoma • Gastric cancer (accelerated approval)
Nivolumab	PD-1	• Advanced/unresectable melanoma after ipilimumab or BRAF inhibitor • NSCLC with progression after platinum • Metastatic renal cell carcinoma • MSI high colorectal cancer • Squamous cell carcinoma head and neck • Hodgkin lymphoma
Atezolizumab	PD-L1	• NSCLC with progression after platinum • Urothelial carcinoma
Avelumab, durvalumab	PD-L1	• Urothelial carcinoma • Merkel cell carcinoma (avelumab)
Ipilimumab/nivolumab	CTLA4/PD-1	• Metastatic melanoma

Checkpoint Inhibitors

SARC 028 Pembrolizumab
Monotherapy for 40 patients each
arm (STS and bone sarcomas)

STS – ORR 18%

Bone – ORR 5%

	Complete response	Partial response	Stable disease	Progressive disease
Soft-tissue sarcomas (n=40)	1 (3%)	6 (15%)	15 (38%)	18 (45%)
Leiomyosarcoma (n=10)	0 (0%)	0 (0%)	6 (60%)	4 (40%)
Undifferentiated pleomorphic sarcoma (n=10)	1 (10%)	3 (30%)	3 (30%)	3 (30%)
Liposarcoma (n=10)	0 (0%)	2 (20%)	4 (40%)	4 (40%)
Synovial sarcoma (n=10)	0 (0%)	1 (10%)	2 (20%)	7 (70%)
Bone sarcomas (n=40)	0 (0%)	2 (5%)	9 (23%)	29 (73%)
Chondrosarcoma (n=5)	0 (0%)	1 (20%)	1 (20%)	3 (60%)
Ewing's sarcoma (n=13)	0 (0%)	0 (0%)	2 (15%)	11 (85%)
Osteosarcoma (n=22)	0 (0%)	1 (5%)	6 (27%)	15 (68%)

Data are n (%).

Table 2: Best response in 80 evaluable patients by sarcoma histological subtype

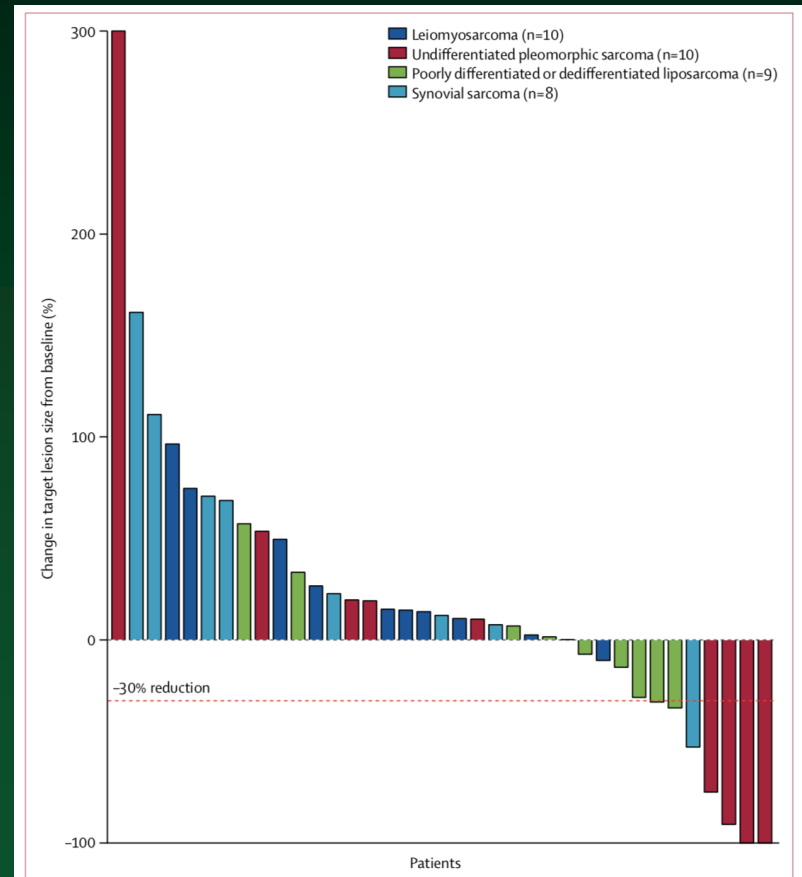


Figure 2: Best percentage change from baseline in size of target lesions in patients with soft-tissue sarcoma
 Tumour sizes were calculated as the sum of target lesion diameters. Data for two patients with synovial sarcoma and one patient with liposarcoma are not shown because they did not have a second scan.

Summary of Response

	Nivolumab (n=38)	Nivolumab + Ipilimumab (n=38)
Best Objective Status (n, %)		
CR	0	2 (5)
PR	3 (8)	5 (13)
SD	15 (39)	19 (50)
PD	20 (53)	10 (27)
Death/No Assessment	0	2 (5)
ORR (Confirmed, CR + PR)	2, 5% (90% CI 1-15%)	6, 16% (90% CI 7-29%)
Clinical Benefit Rate (CR + PR + SD)	18% (90% CI 1 - 32%)	29% (90% CI 17-43%)

All grade 3/4 TRAE (14% vs 7%), lower than melanoma (54%)

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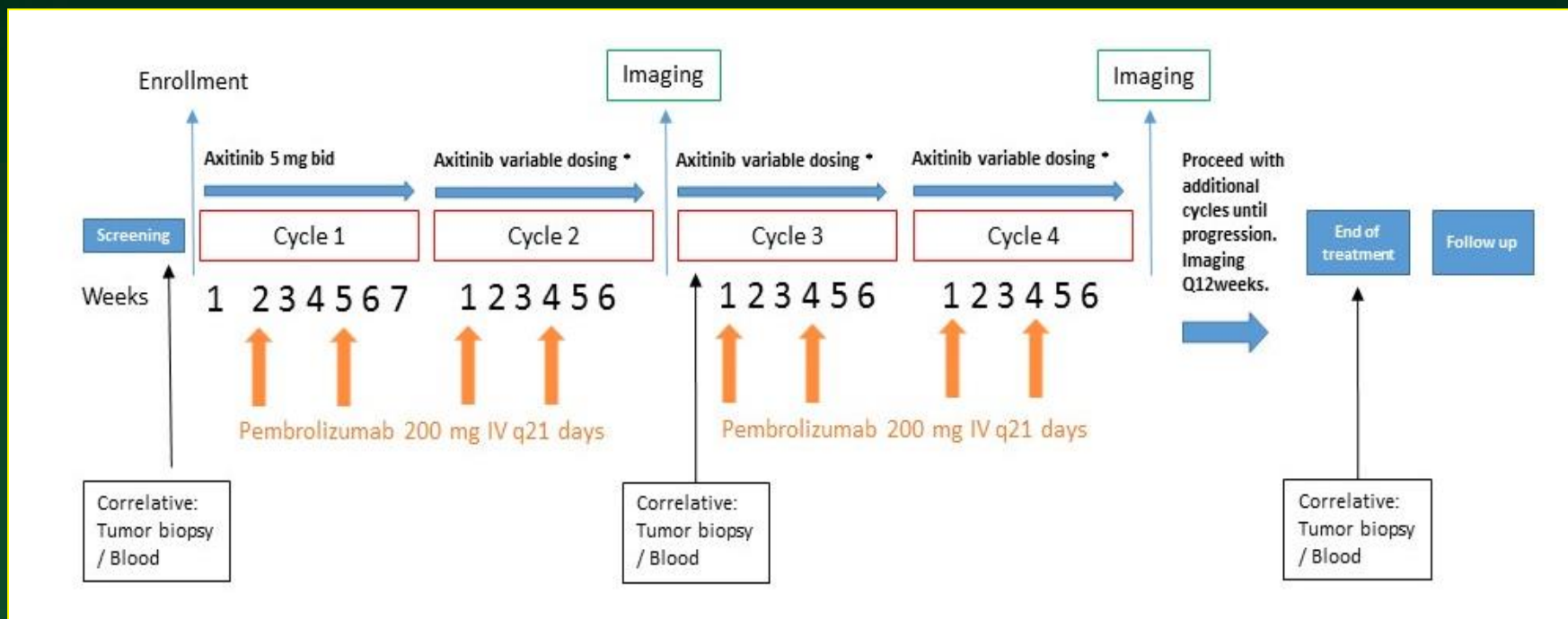
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Selected checkpoint combinations

Agents	Target
IDO inhibitor plus pembrolizumab (pending)	Treg
Metronomic Cytosan + pembrolizumab NCT02406781 (ASCO17)	Treg
Axitinib plus pembrolizumab (NCT02636725)	VEGF
Sunitinib plus nivolumab (IMMUNOSARC, pending)	Multi-TKI
Imatinib plus ipilimumab (NCT01738139)	Multi-TKI
Liposomal IL-2 + pembrolizumab (pending)	Innate immunity
PLX3397 + pembrolizumab (NCT02452424)	Macrophage
PLX3397 + sirolimus (NCT02584647)	Macrophage
SARC032 Neoadjuvant XRT +/- pembrolizumab (NCT03092323)	Neoantigens
Neoadjuvant Durvalumab + tremelimumab + radiation (NCT03116529)	Neoantigens
Doxorubicin + pembrolizumab (NCT02888665)	Neoantigens

Axitinib plus pembrolizumab

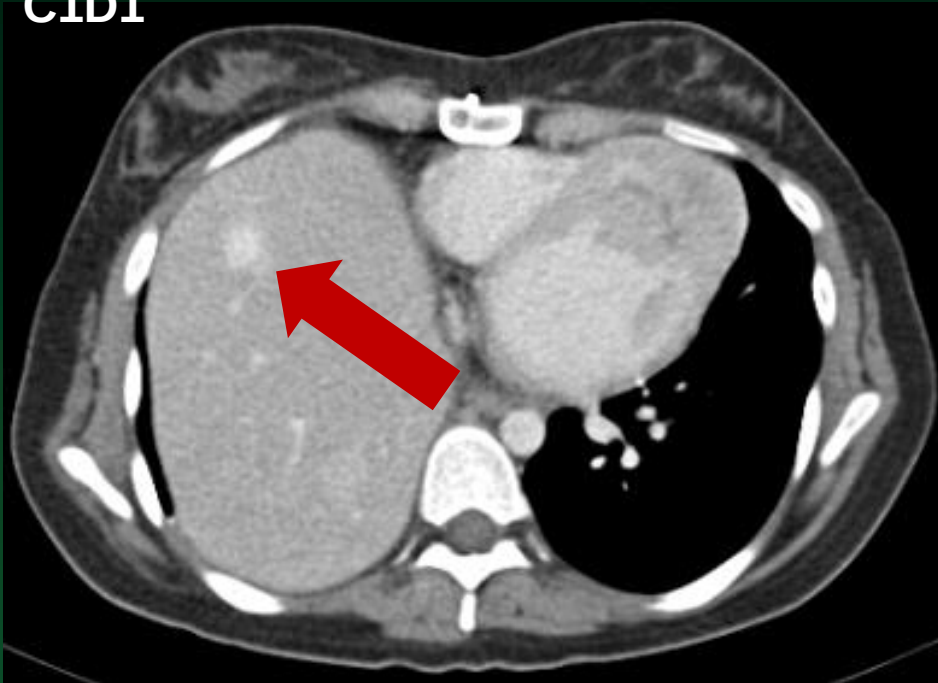
- Single arm, open-label, single institution, investigator-initiated
- Phase II trial of 30 patients with advanced/metastatic STS enriched for ASPS – fully accrued



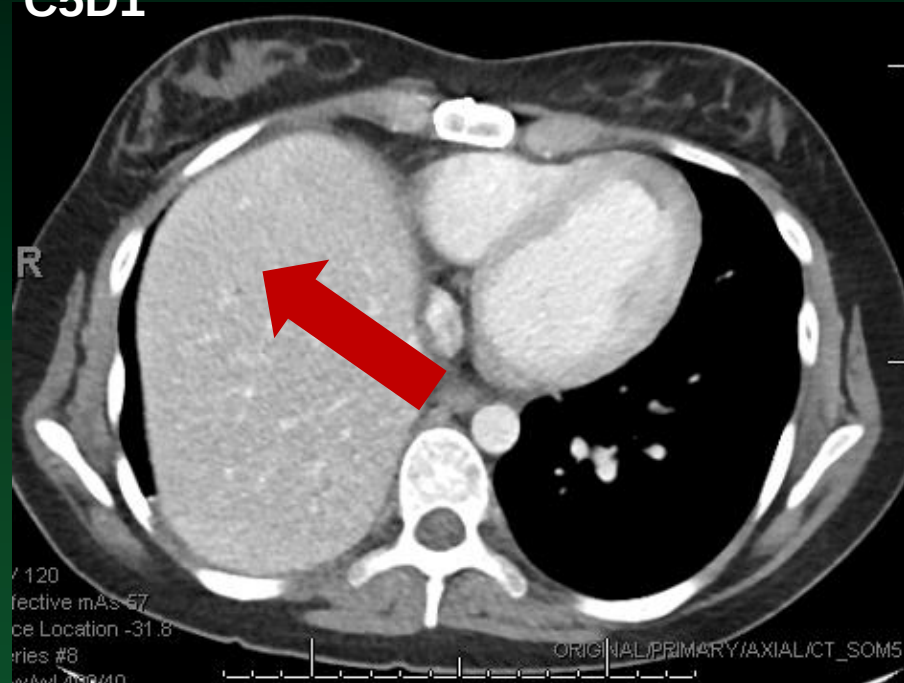
Dose escalation/de-escalation permitted of axitinib based on tolerance
NCT02636725, PI Wilky

Responding ASPS patients

C1D1



C5D1

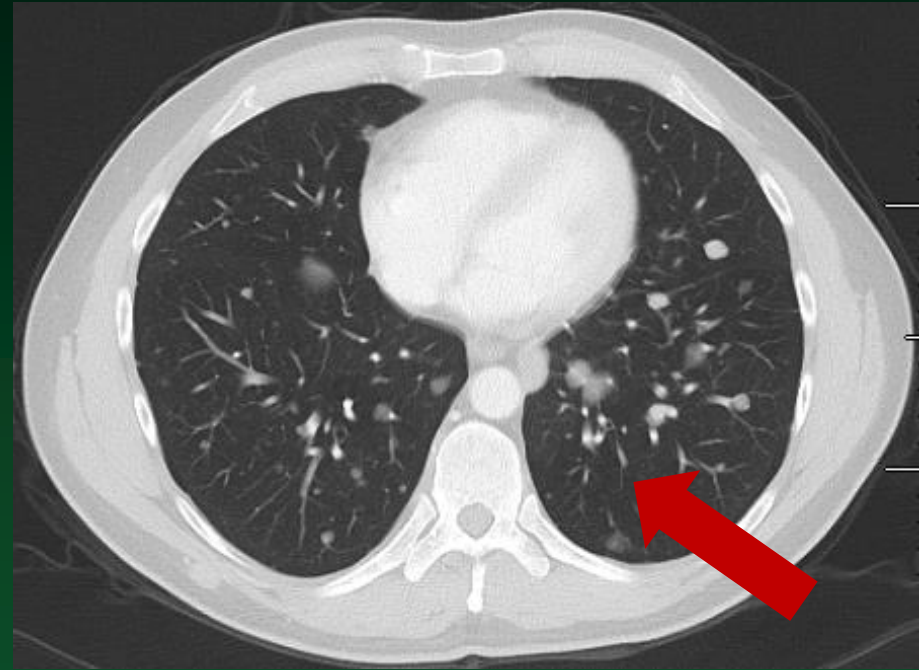


Progressed on sunitinib prior to study

Responding ASPS patients

C1D1

C5D1



Progressed on sunitinib prior to study

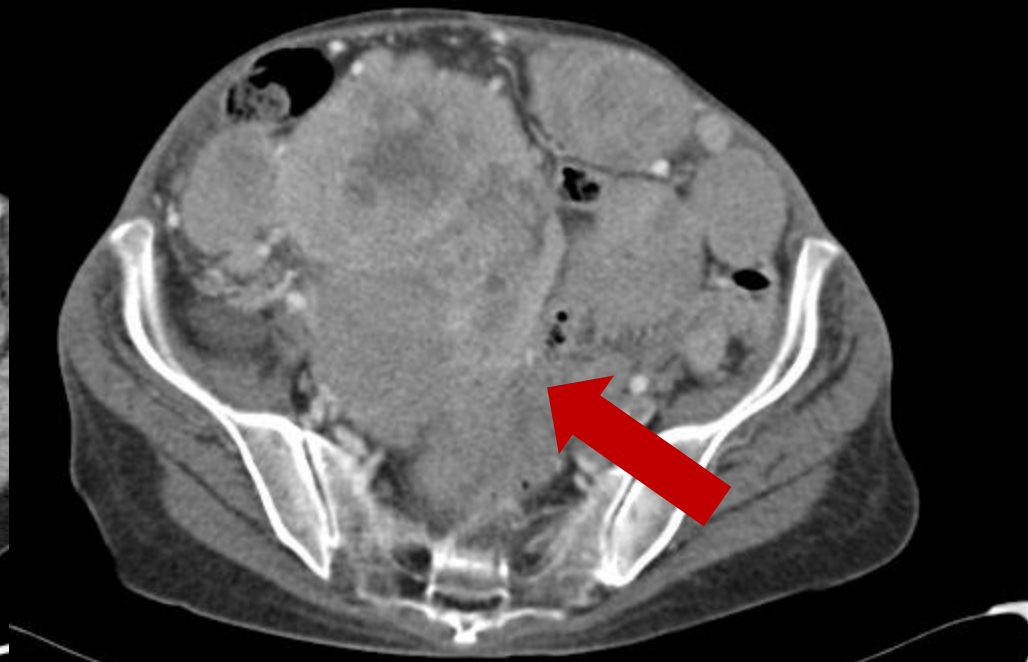
57 year old with LMS

Treatment history

- Adria/ifex x 6 cycles 12/2010
- 4 cycles of gem/tax and 2 cycles of single agent gemcitabine 3/7/11
- Recurrence: 4 cycles gemcitabine 900mg/m² and pazopanib 800mg daily 8/18/14-11/13/14
- Adria 75mg/m²/ + dacarbazine 750mg/m² x 4 cycles beginning 11/2014
- 6 cycles of trabectedin on 12/1/15
- 2 cycles of adria/dacarbazine from 12/2015-1/2016
- Combination immunotherapy with ipilimumab and nivolumab - Progression
- Olaparib 8/27/16- Progression
- Affinitor 9/16-11/29/16 with Progression

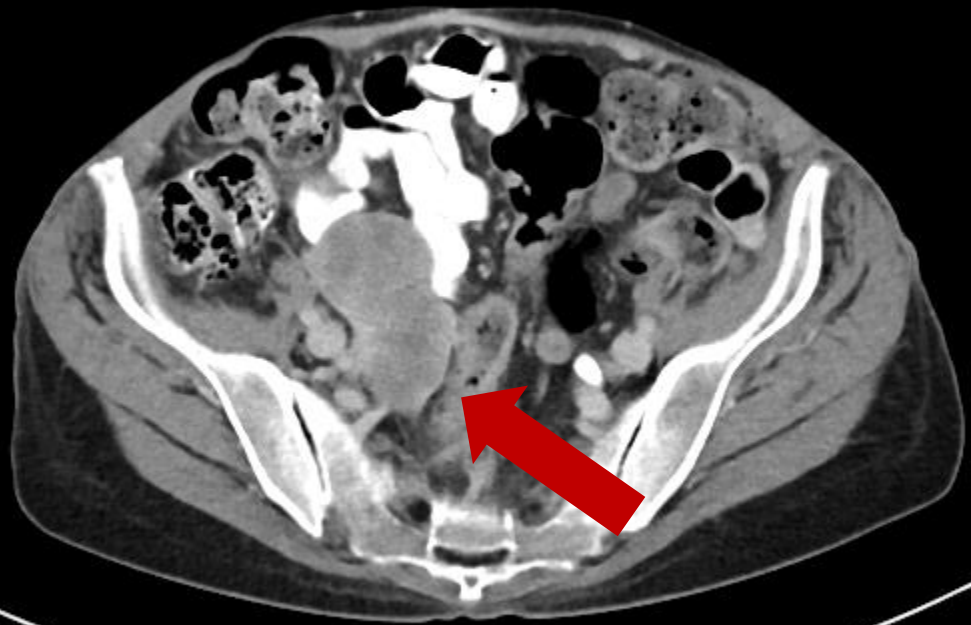
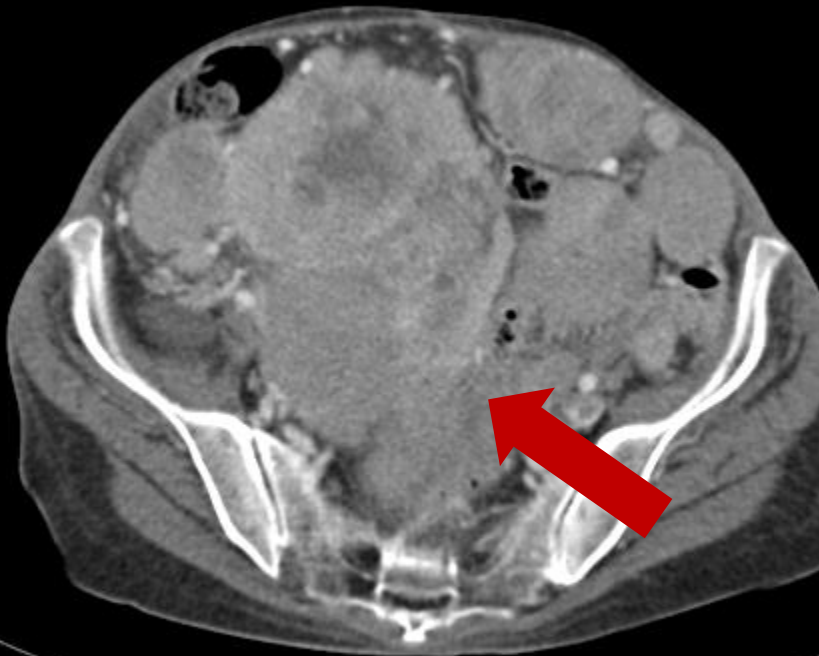
Targeted therapy

mTOR inhibitor



Chemotherapy

Ifosfamide 6 cycles



Dendritic Cell Vaccine Trial *With Resection*



6/22/17



1/22/17

Sylvester Comprehensive Cancer Center

Sarcoma Team

- **Medical Oncology**

- Jon Trent
- Breelyn Wilky
- Matteo Trucco (Pediatric)

- **Pathology**

- Andrew Rosenberg
- Darcy Kerr

- **Clinical Research**

- Georges Tahhan
- Tamara Leon
- Jeena Solomon
- Lei Zhang

- **Lab Research**

- Josienne Eid
- Joanna DeSalvo
- Luyuan Li
- Karina Galoian

- **Radiology**

- Ty Subhawong
- Jean Jose

- **Nurse-Practitioner**

- Morgan Smith

- **Nursing**

- Eryka Lacayo
- Yolanda Roper

- **Social Work**

- Marlene Rodriguez

- **Interventional Radiology**

- Raj Narayanan
- Shree Venkat

- **Gynecologic Oncology**

- Brian Slomovitz
- Matt Pearson
- Marilyn Huang

- **Orthopedic Oncology**

- Sheila Conway
- Frank Eismont
- Juan Pretell
- Mo Al Maaieh

- **Surgical Oncology**

- Nipun Merchant
- Alan Livingstone
- Danny Yakoub

- **Radiation Therapy**

- Raphael Yechieli
- Laurea Freedman
- Aaron Wolfson

- **Head & Neck Surgery**

- Zoukaa Sargi
- Frank Civantos

- **Thoracic Surgery**

- Dao Nguyen
- Nestor Villamizar

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