University of Colorado **Anschutz Medical Campus**

Translational Immunotherapy for Rare Diseases

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Disclosures

- **Consulting/Advisory Role**

  Springworks, Deciphera, Adaptimmune, Daiichi Sankyo, Epizyme, Adcendo, Polaris, Boehringer Ingelheim

- **Research Funding**

  Agenus, Exelixis

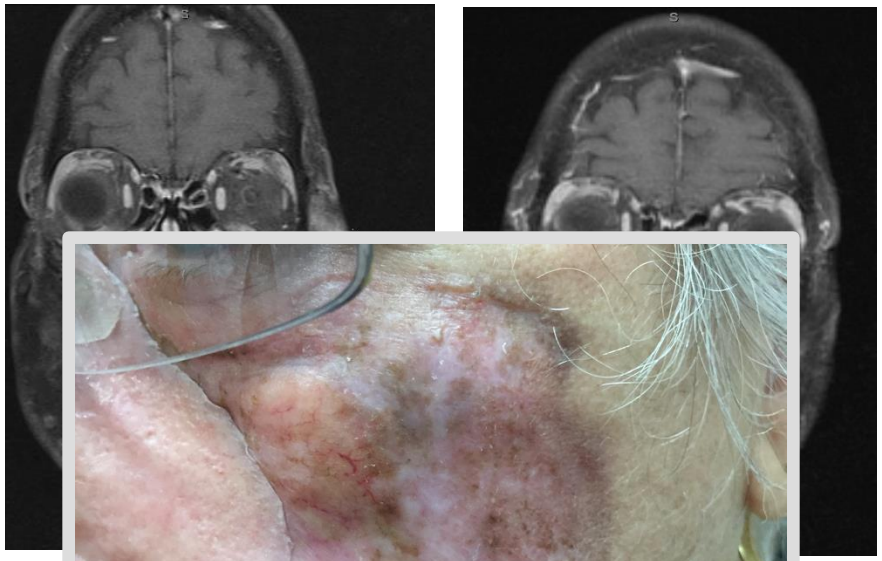
Some of what I'm discussing is investigational…

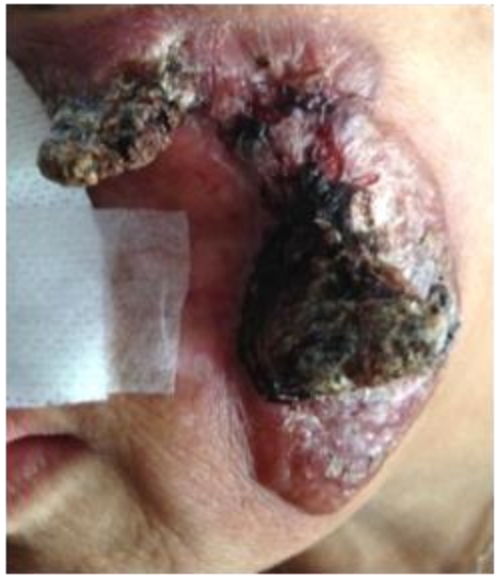
Take home messages

- Clinical trials are critical for rare diseases like sarcomas
- Despite historical challenges to clinical trials for rare sarcomas, new drugs are being approved
- Partnerships between patients, researchers, patient advocacy groups, FDA, and pharma are critical
- Learning from every patient in trials through laboratory research is critical

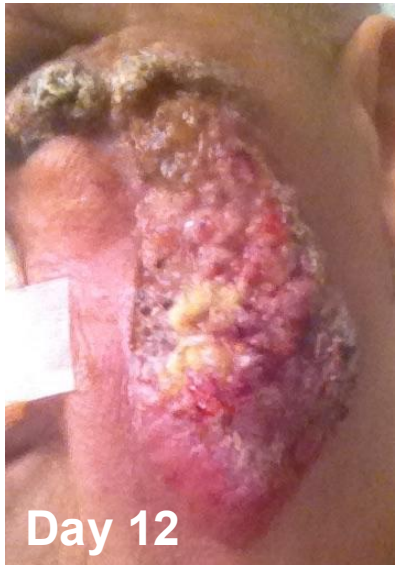
My first immunotherapy super-responder.

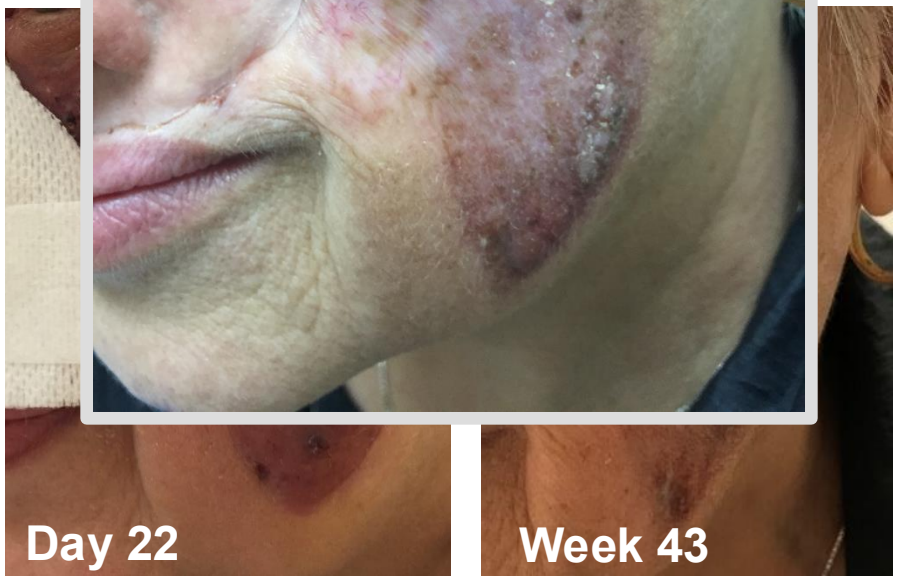
- Treated with AGEN1884 (anti-CTLA-4) on Phase 1 trial at dose level 1 – **0.1 mg/kg** every 3 weeks x 18 months
- Radiographic complete response since March 2017, path CR confirmed February 2018 – remains cured!
- Remarkable responses in cutaneous angiosarcoma with checkpoint inhibitors in retrospective case series





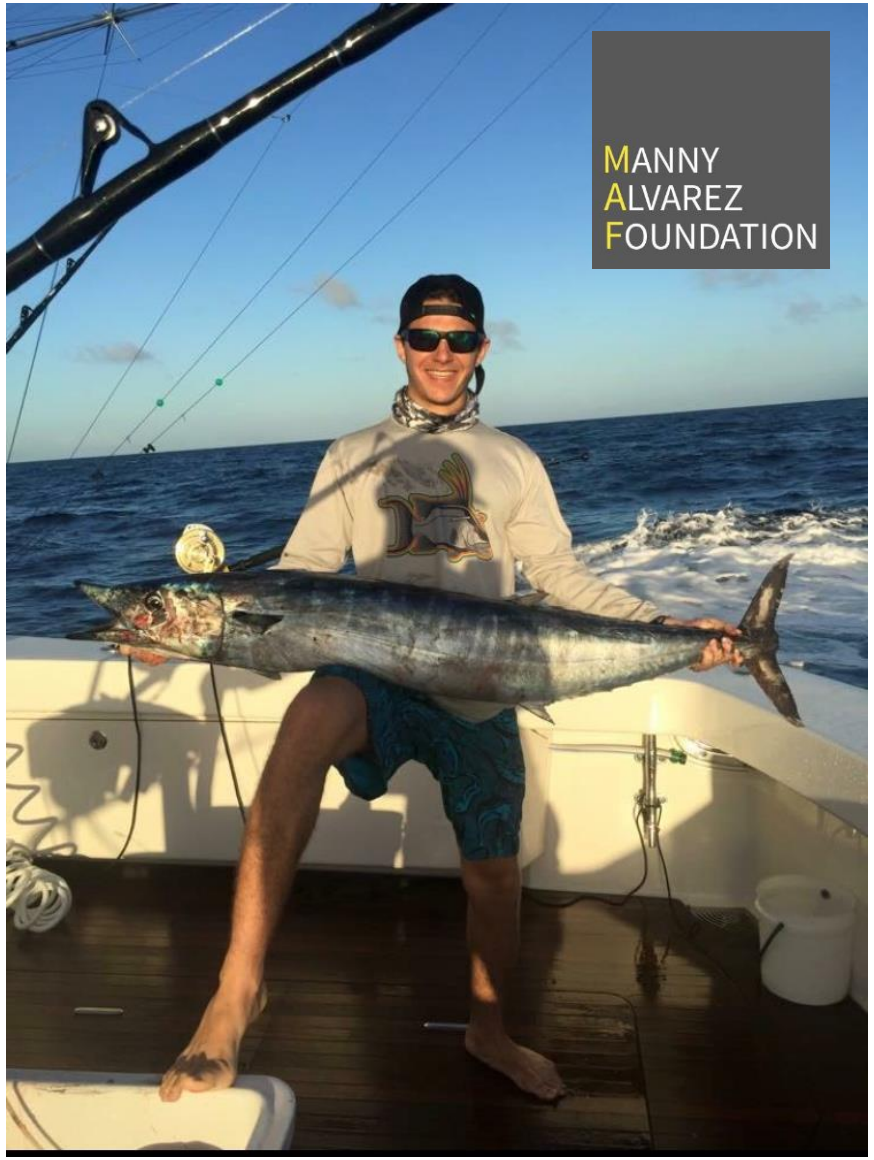
Baseline

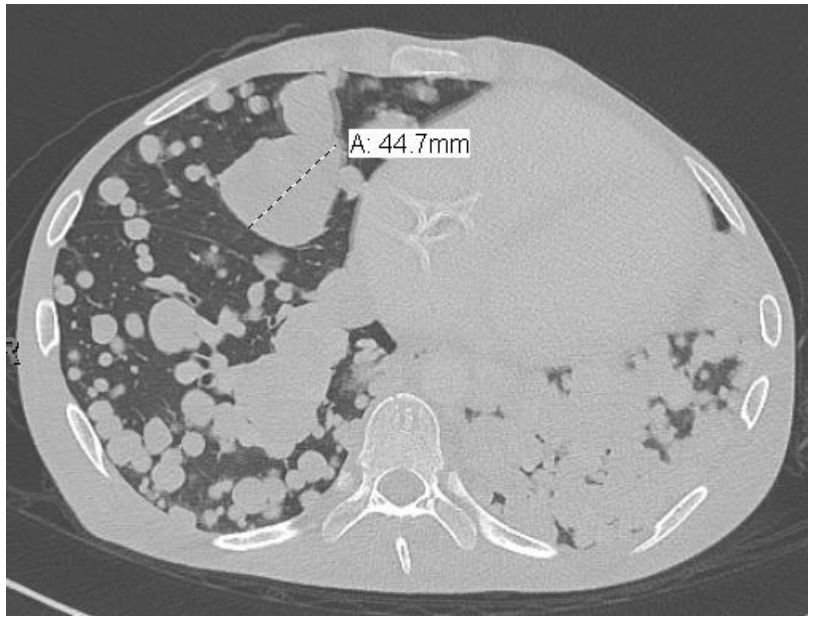




Florou…Wilky et al, JITC 2019

The patient that I couldn't save.

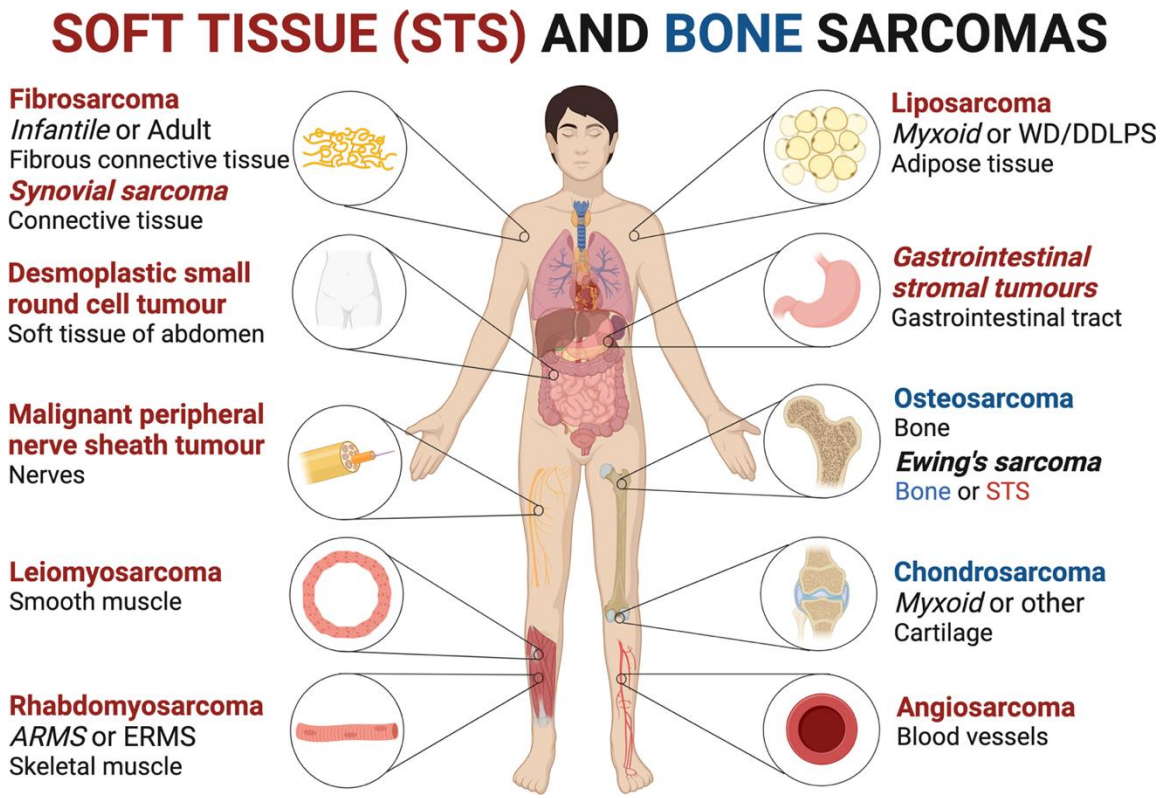


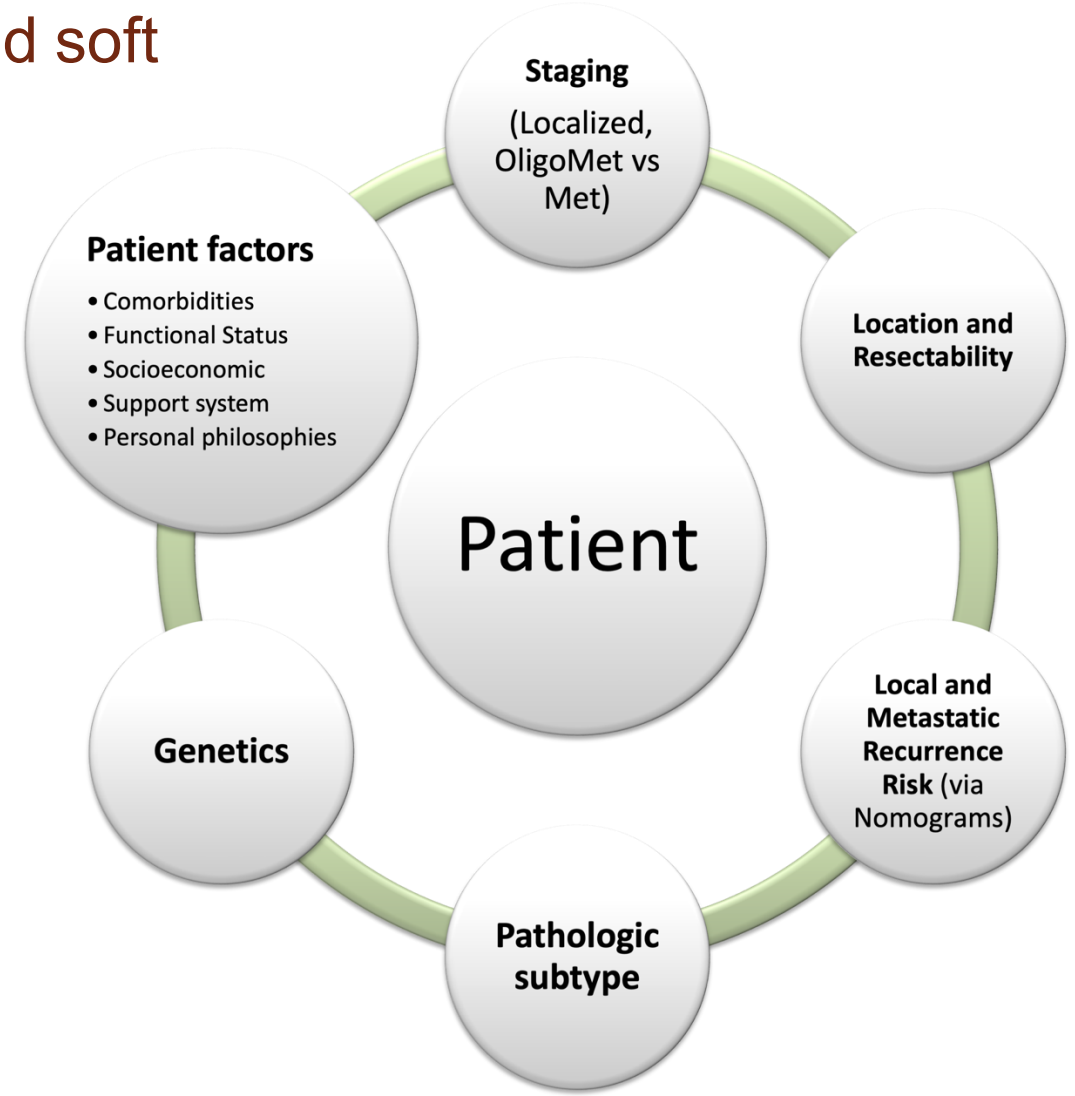


- 23 yo M with metastatic alveolar soft part sarcoma
- Led to axitinib-pembrolizumab IIT that went on to show >50% response rate in ASPS patients
- ASPS now is the most responsive sarcoma subtype with an FDA approval for atezolizumab
- Best response of stable disease on PD-L1 trial at MDACC
- He survived long enough to get one dose of treatment on the clinical trial he inspired

Sarcoma Principles – Know the sarcoma… and know the patient.

- 100+ different histologic subtypes of bone and soft tissue neoplasms (but 1% of adult cancer!)



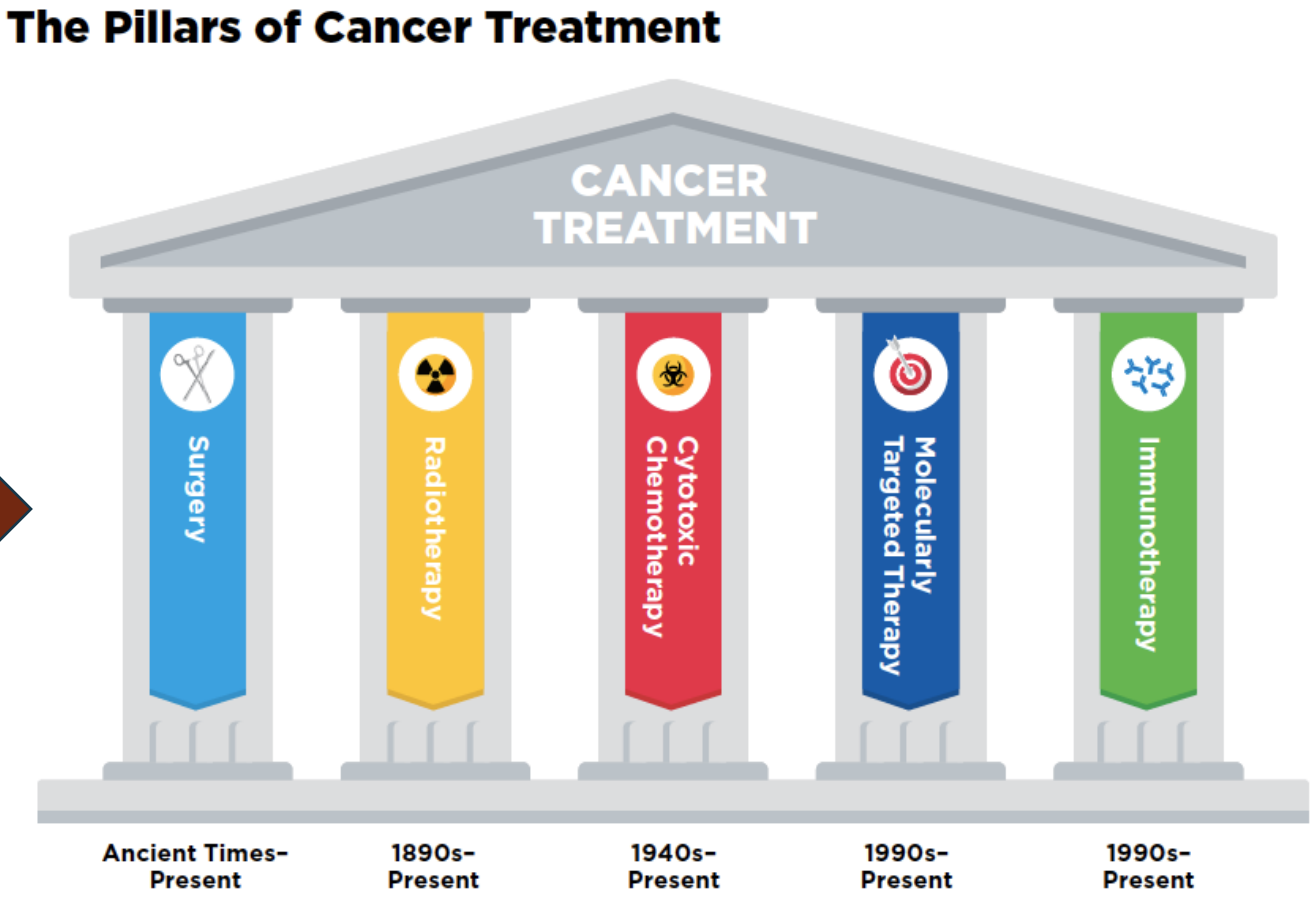


High-grade undifferentiated pleomorphic sarcomas (UPS) – mesenchymal stem cells

Wilky et al, ASCO SEP 2022

Sarcoma Principles – 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
- Reproductive endocrinology (fertility)
- Social workers/psychologists



AACR Cancer Progress Report 2023

Doxorubicin is standard of care chemotherapy for sarcomas since the 1970s…

Doxo monotherapy study arm (comparator)	Year	mPFS mo (95% CI)	mOS mo (95% CI)	Response Rate / CBR
Judson (doxo+ifos)[1]	2014	4.6 (2.9-5.6)	12.8 (10.5-14.3)	14% (59%)
Ryan (palifosfamide)[2]	2016	5.2 (4.2-6.0)	16.9 (14.8-22.9)	20% (41%)
Tap (olaratumab Ph II)[3]	2016	4.1 (2.8-5.4)	14.7 (9.2-17.1)	12% (61%)
Seddon (gem+tax)[4]	2017	5.8 (4.6-7.6)	19.1 (15.0-22.8)	19% (67%)
Tap (evofosfamide)[5]	2017	6.0 (4.6-6.2)	19.0 (16.2-22.4)	16% (66%)
Tap (olaratumab Ph III, *8 cycles)[6]	2020	6.8	19.7	18% (76%)
Doxorubicin-Pembro[7]	2020	8.1 (7.6-10.8)	27.6 (18.7-NR)	19% (80%)
Doxorubicin-Pembro[8]	2021	5.7	17.0	37% (80%)

1. Judson et al, Lancet Oncol 2014. 2. Ryan et al, JCO 2016. 3. Tap et al Lancet 2016. 4. Seddon et al, Lancet Oncol 2017. 5. Tap et al, Lancet Oncol 2017. 6. Tap et al, JAMA Oncol 2020. 7. Pollack et al, JAMA Oncol 2020. 8. Livingston et al, Clin Cancer Res 2021.

Modified from Wilky, ASCO 2019 discussion

Other combinations/agents have not improved outcomes over doxorubicin

Drug	RR (%)	PFS (median, months)	OS (median, months)	Included histologies
Doxorubicin	18.3	6.8	19.7	Most subtypes, soft tissue (Tap, 2019)
Doxorubicin/trabectedin	NR	12.0	33.0	LMS only
Liposomal doxorubicin	10	2.1	10.6	Most subtypes including LMS, HGUPS, AS, SS (Judson I, 2001)
Doxorubicin/ Ifosfamide	26	7.4	14.3	Most subtypes including LPS, SS, MFS, Pleomorphic RMS, UPS (Sheng JY, 2016)
Gemcitabine/ Docetaxel	17	6.2	17.9	All subtypes esp. AS, LMS. HGUPS (Maki 2007)
Trabectedin	9.9	4.2	12.4	FDA approved only for LPS and LMS (Demetri 2016)
Eribulin	4	2.6	13.5	FDA approved only for LPS (Schoffski 2016)
Pazopanib	6	4.6	12.5	All subtypes except LPS (van der Graaf 2012)

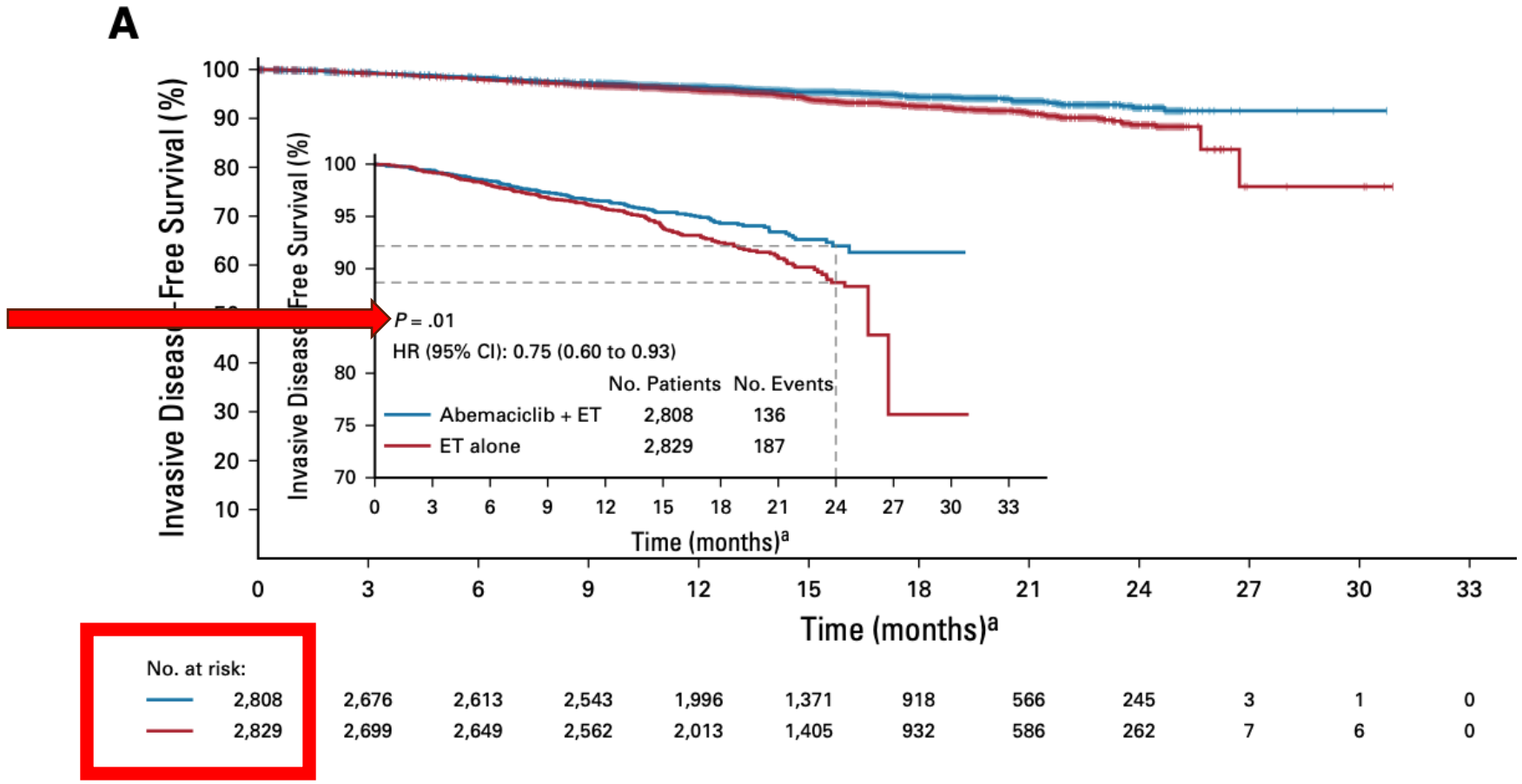
Adapted from Alavi…Wilky et al, Discov Med 2018
Pautier et al, NEJM 2024

Why is it so difficult to approve new therapies?

- **Historically, large phase 3 trials have included multiple subtypes of sarcomas (a one-size fits all approach)**
- **This has been the strategy to overcome rarity and funding limitations**
  - Need large numbers of patients for a phase 3 trial
  - Expensive!
  - Pharma priorities typically have not included sarcomas

To illustrate this point -

A representative breast cancer Phase 3 trial… for HR+, HER2-, Node-Positive, High risk…

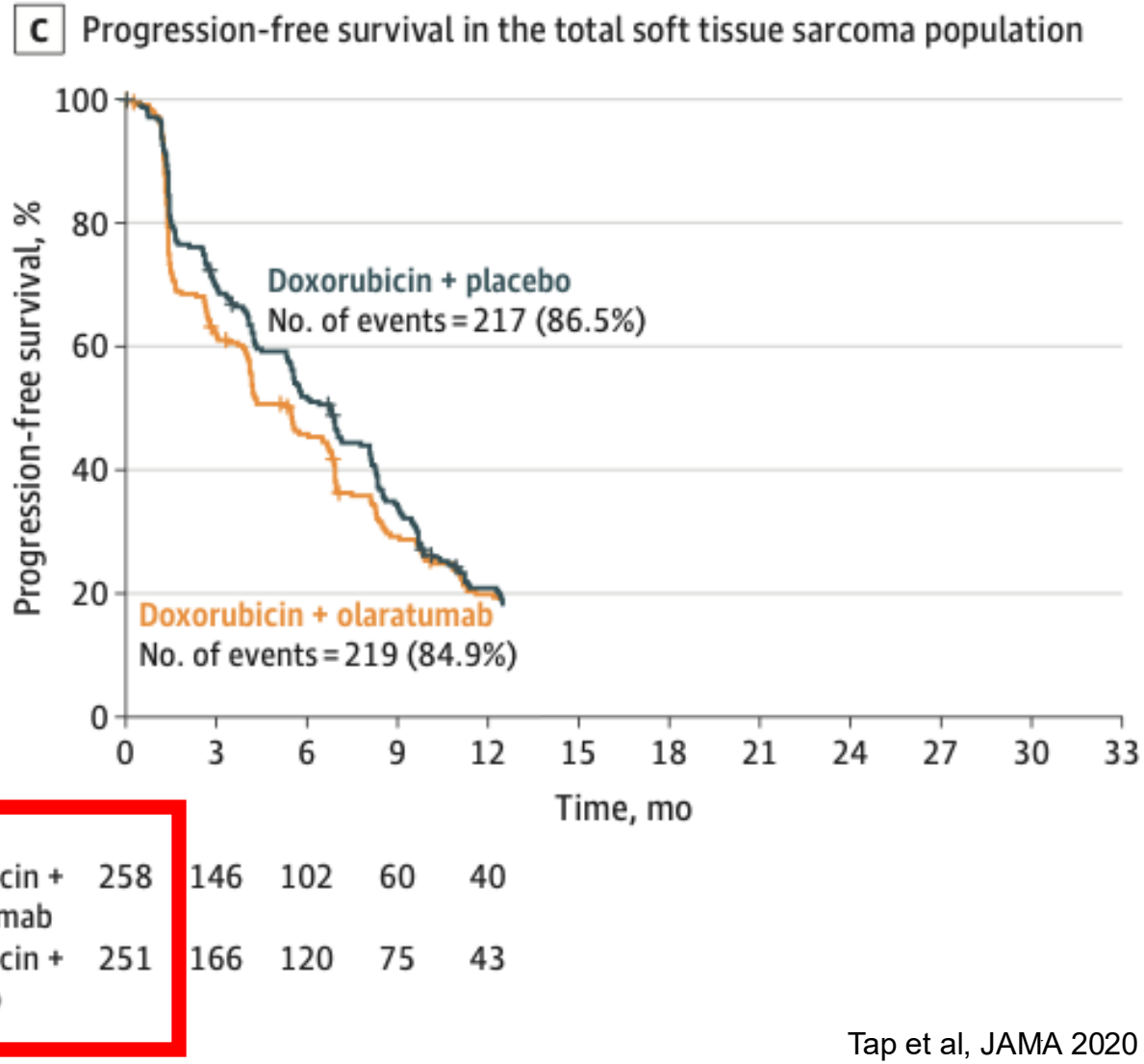


Johnston et al, JCO 2020

The most famous failed Phase 3 trial in sarcoma…

- A Phase 2 trial showed very strong overall survival benefit with doxorubicin plus anti-PDGFR antibody olaratumab
- Mechanism wasn't clear…
- Accelerated approval
- Failed Phase 3 leading to ASCO plenary presentation and withdrawal of drug

Histology		
Leiomyosarcoma	119 (46.1)	115 (45.8)
Liposarcoma	48 (18.6)	43 (17.1)
Pleomorphic sarcoma	34 (13.2)	30 (12.0)
Other[d]	57 (22.1)	63 (25.1)



Tap et al, JAMA 2020

BUT – we can do it. How?

- Collaboration is essential to conduct clinical trials in ultra-rare diseases (ONE sarcoma, not multiples).
- Rationally designed treatment based on well-understood mechanism
- FDA has been willing to approve therapy for rare diseases based on strong Phase 2 data when conducting a Phase 3 trial is not feasible
- New FDA pathways for rare diseases have generated interest by pharma

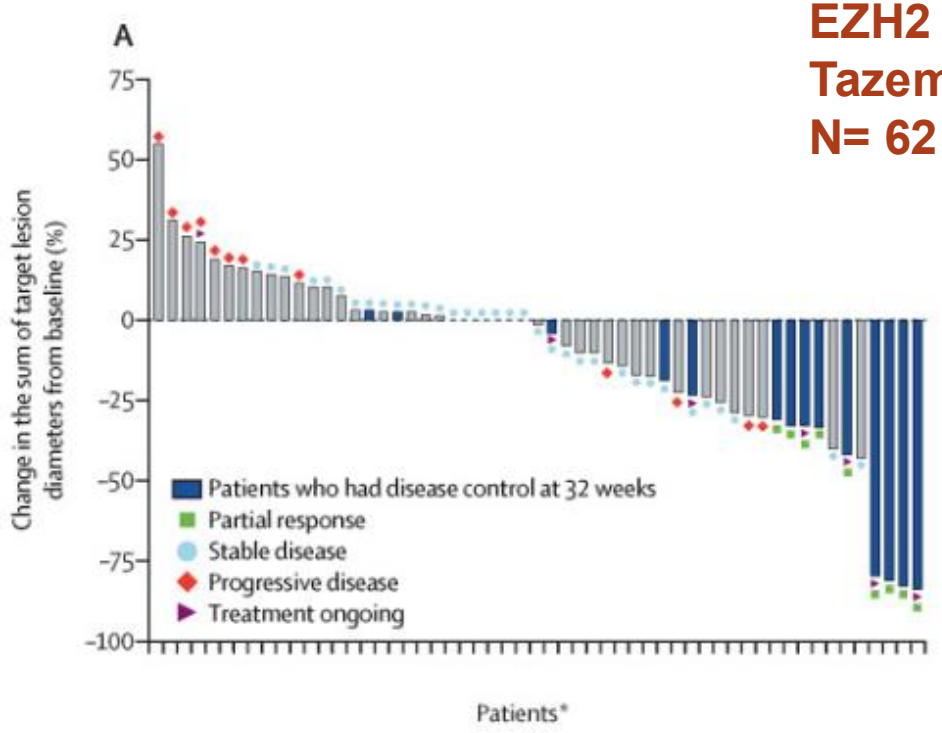
Sarcoma subtype	Genetic Driver	Agent
Alveolar soft part sarcoma	ASPL/TFE3	Atezolizumab, anlotinib
PEComa	TSC1/TSC2 muts.	Nab-sirolimus
Desmoid fibromatosis	CTNNB1, APC muts.	Nirogacestat, AL-102
Giant cell tumor of bone	RANKL	Denosumab
Plexiform neurofibromas	NF1	Selumetinib, mirdametinib
PVNS/TGCT	Collagen/CSF1 trans.	Pexidartinib, vimseltinib
Inflammatory myofibroblastic tumor	ALK fusions	Crizotinib
Dedifferentiated liposarcomas	MDM2, CDK4 amp	Abemaciclib
Epithelioid sarcoma	INI1 loss	Tazemetostat
Chondrosarcomas	IDH1/IDH2 mutations, DR5	Ivosedinib, INHIRBX-109
Synovial sarcomas/Myxoid LPS	MAGE-A4/NY-ESO expression	Afami-cel, Lete-cel

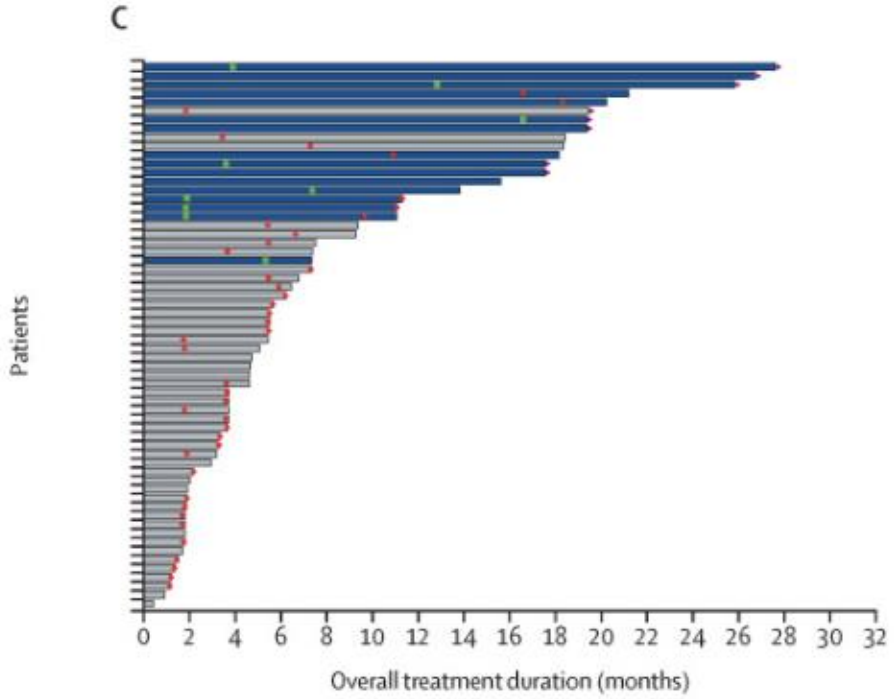
(approved, ongoing reg. trial)

Epithelioid sarcoma

- **Incidence – 0.3-0.5 / 100,000 people**
- **Target – SMARCB1/INI1 loss**

EZH2 inhibitor – Tazemetostat
N= 62 patients





Response rate 15%

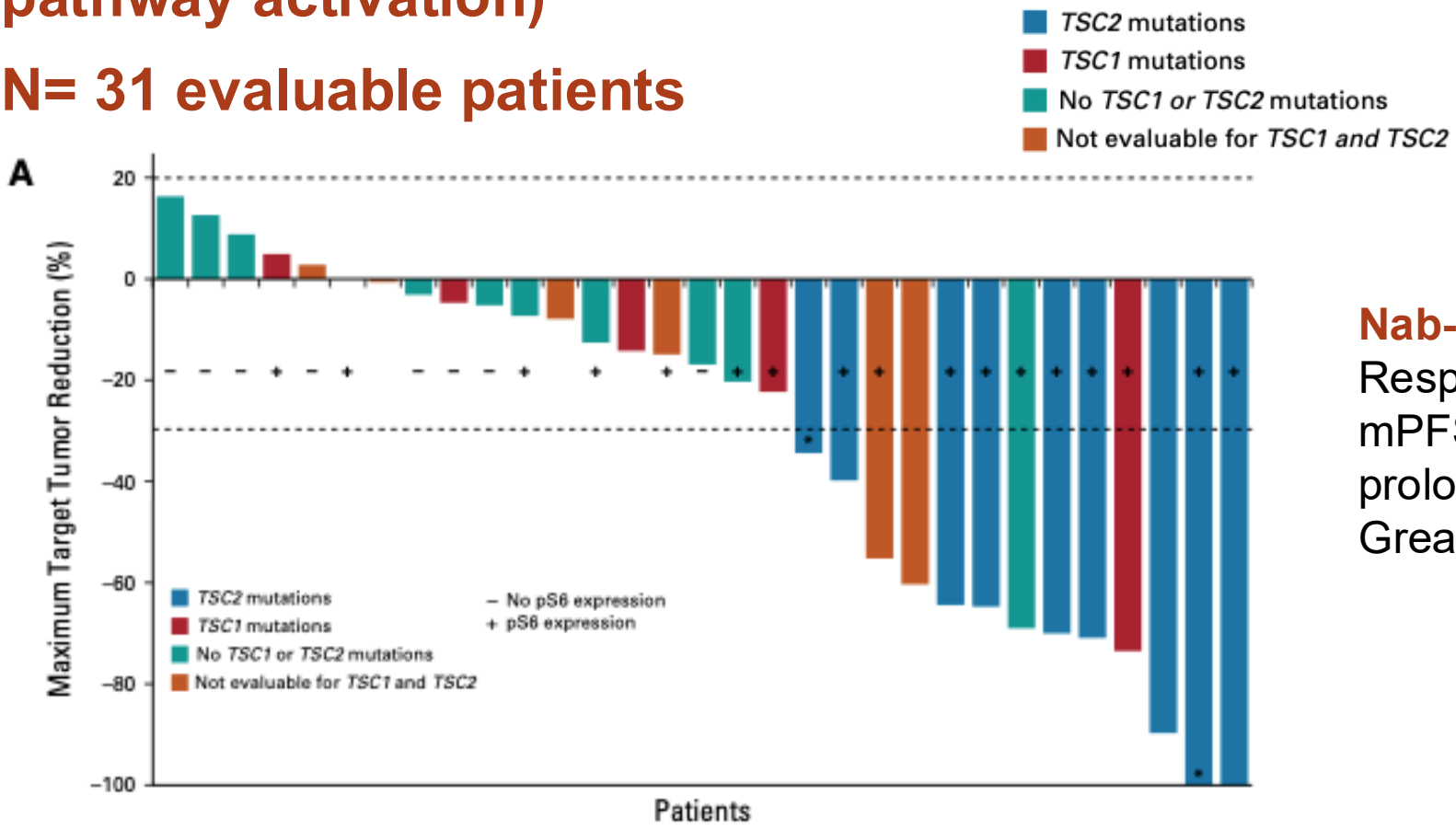
Median PFS 5.5 months but some patients with long term stable disease (24% received for longer than 12 months)

Minimal toxicity

Gounder et al, Lancet Oncol 2020

PEComa

- **Incidence – 0.12 to 0.24 per million people**
- **Target – TSC1 or 2 mutations (mTOR pathway activation)**
- **N= 31 evaluable patients**



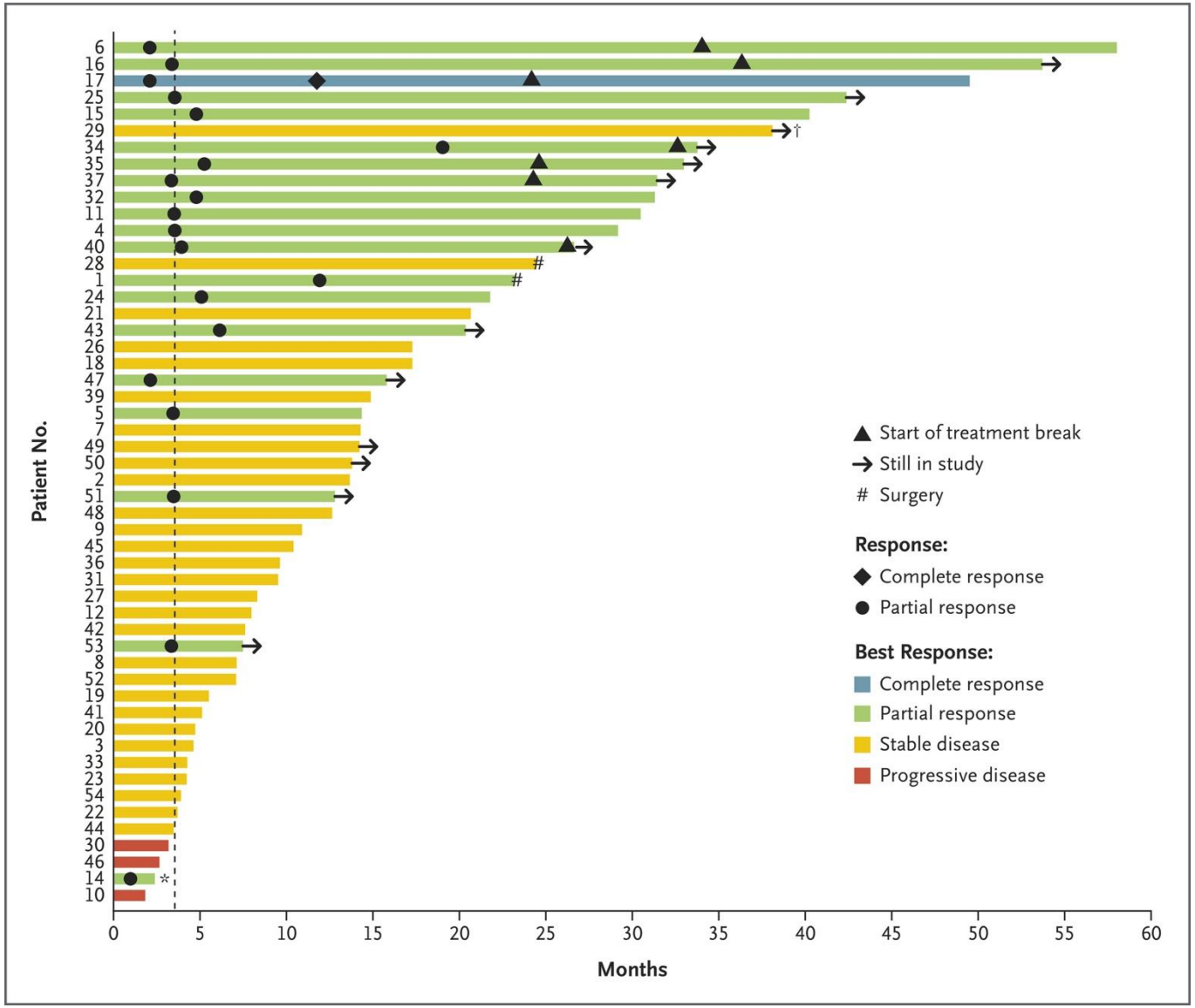
Nab-Sirolimus –
Response rate 39%
mPFS 10.6 months, can have prolonged DoR up to ~ 4 years
Greater benefit in TSC2 mutations

Wagner et al, JCO, 2021

Alveolar soft part sarcoma

- Global incidence of less than 1 in a million persons
- Atezolizumab: PD-L1 blockade

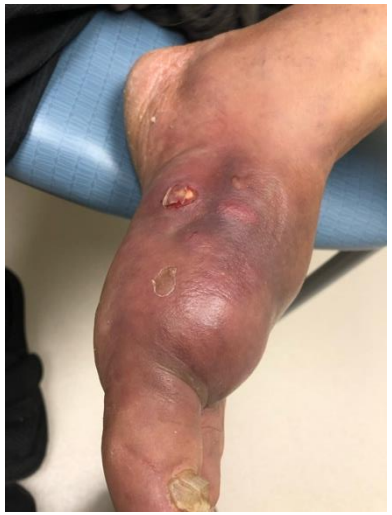
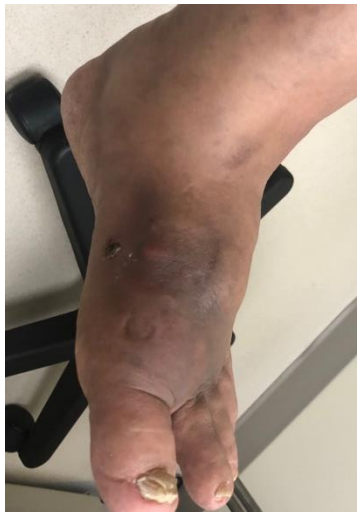
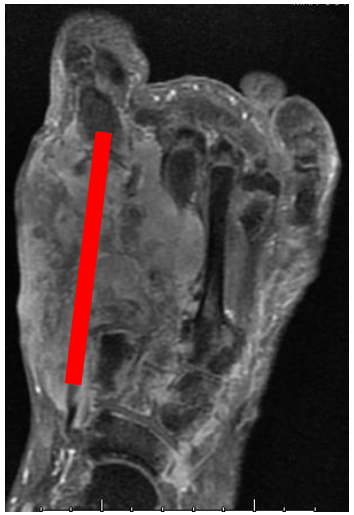
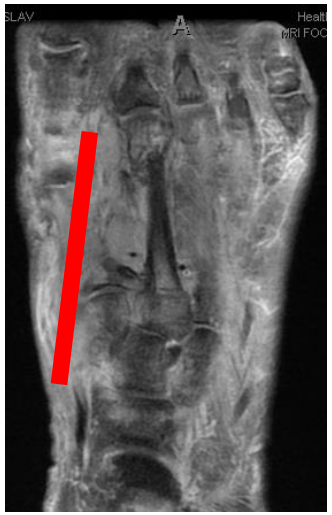
N=52
37% response rate
mPFS 20.8 months



Chen et al, NEJM 2023

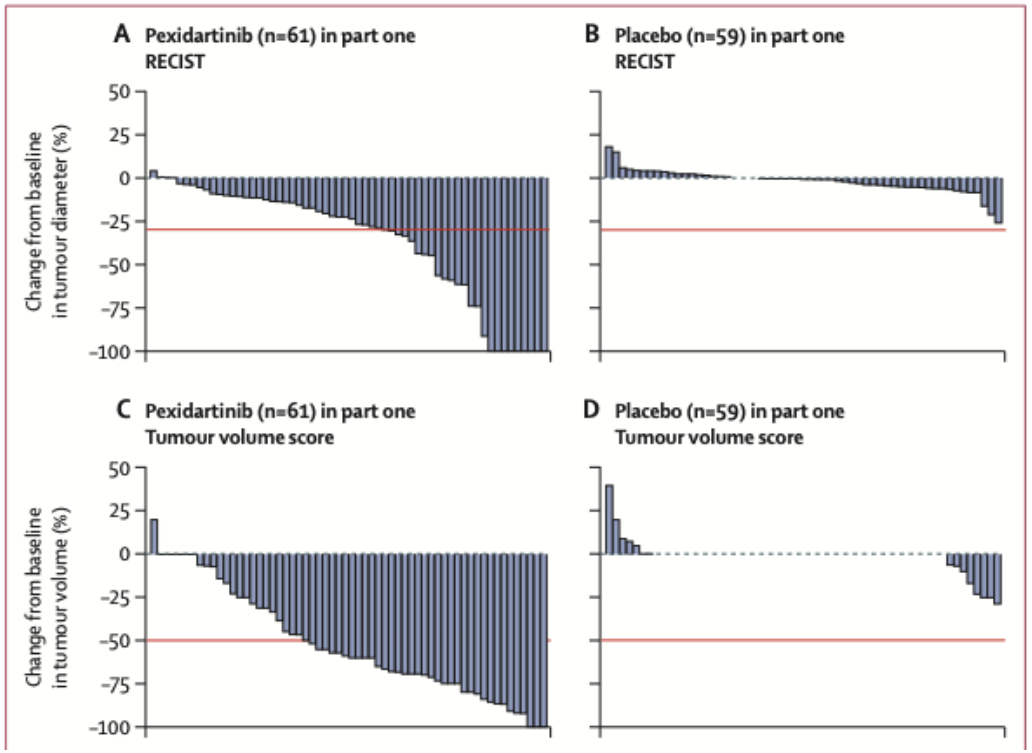
Why is it so difficult to approve new therapies?

- **Traditional endpoints of clinical trials may under-estimate benefit in sarcomas**
  - Response rate (tumor shrinkage) of more than 20% typically required for “benefit”
  - To qualify as a shrinkage RECIST requires longest diameter to decrease by 30%

TGCT – pexidartinib and vimseltinib

- Response rate – 39% by RECIST, and 56% by tumor volume score
- Significant improvements in range of motion and quality of life scores (pain, physical function and stiffness)



Tap et al, Lancet 2019

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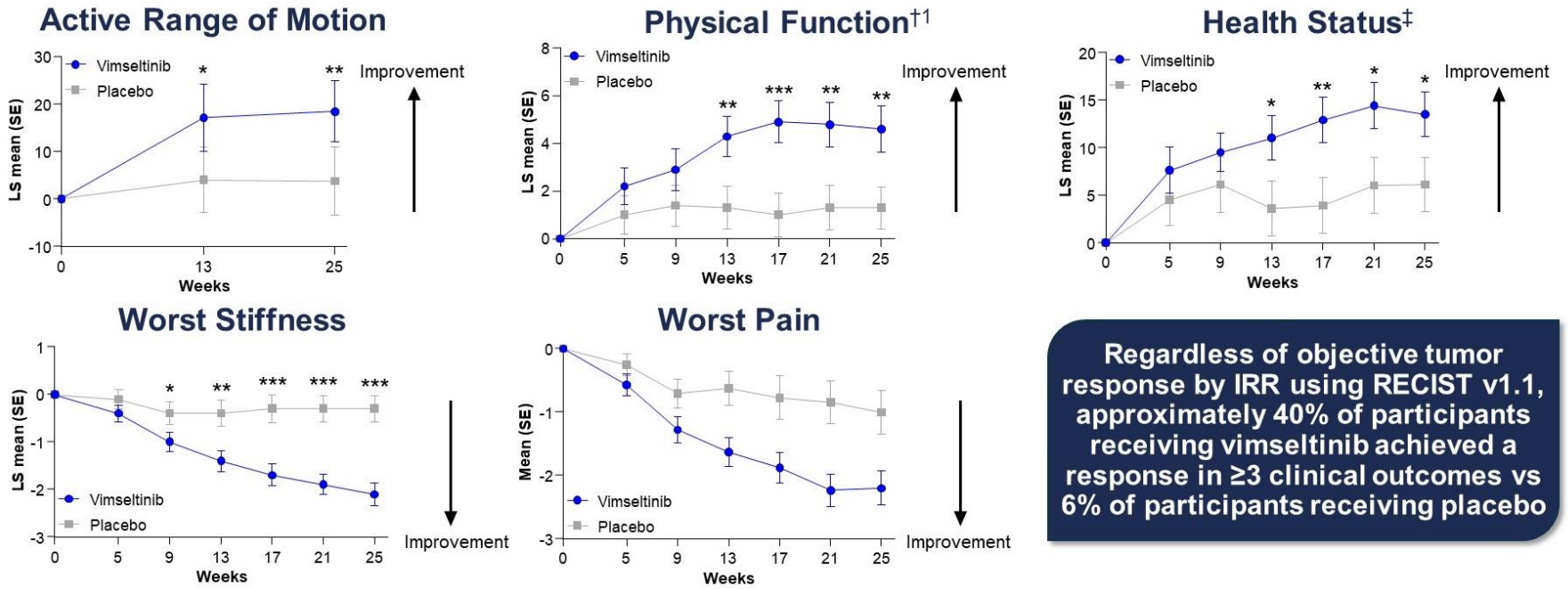

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Tap et al, ASCO Annual Meeting 2024
Gelderblom et al, Lancet 2024

How do we find and recruit patients with rare diseases?

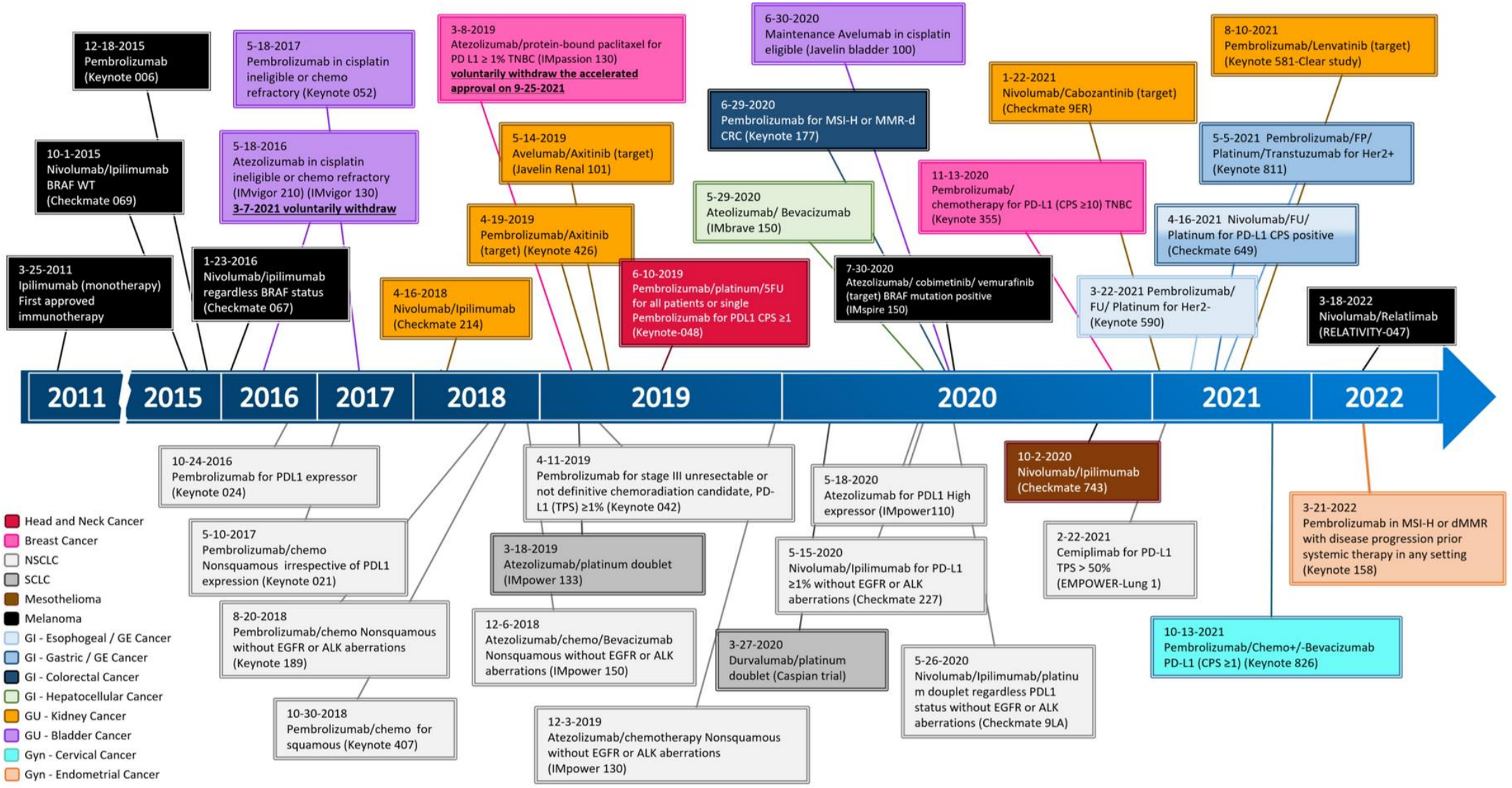
Patient advocacy groups and foundations are critical partners!!!

- Internet based to reach patients globally
- Input for clinical trial design
- Directing patients to sarcoma centers and raising awareness of ongoing clinical trials
- Funding support for patients to travel for clinical trial participation
- Research grants and direct support to sarcoma studies

So how do we FIND new treatments?

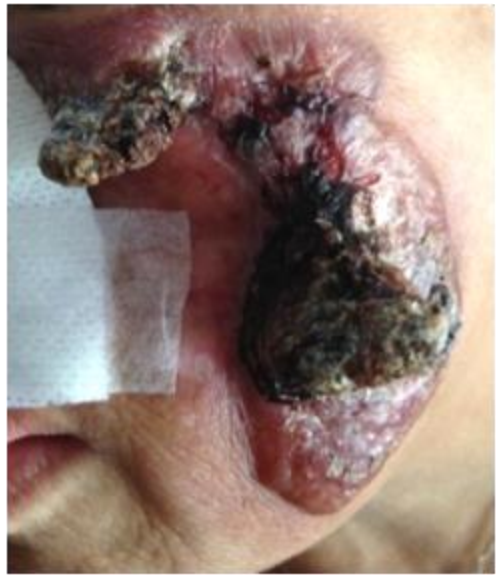
- **We have the methodology and precedent to get approvals done…**
- **We have the patients and the networks to recruit them…**
- **How do we generate the next clinical trials?**
- **Challenges to lab-based research…**
  - Lack of funding
  - Lack of models – especially for immunotherapy
  - Collaboration between clinicians and scientists is key… and translational researchers who do both are critical

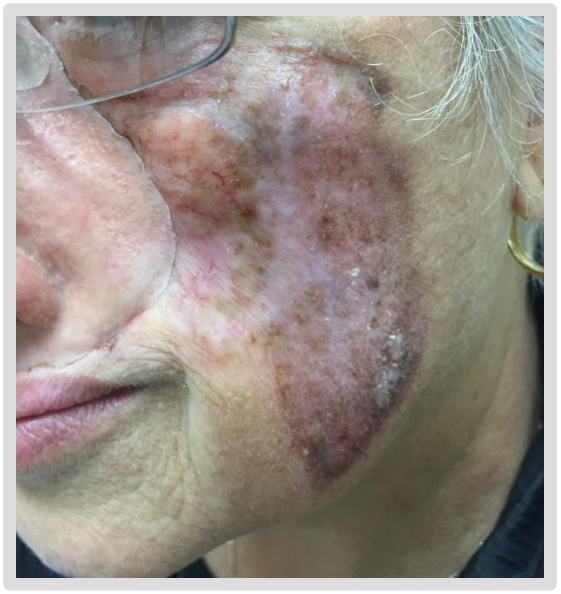
Immunotherapy has changed cancer therapy forever



Ma et al, Exp Hematol Oncol 2023

Sarcoma immunotherapy responders





Responders:

- UPS[1-5,9]
- dLPS[1,2]
- ASPS[5-7]
- SMARCA-4 deficient (malig rhabdoid tumor, epithelioid sarcoma)[6,7]
- Chordomas[5,6]
- Cutaneous angiosarcomas[3,5,8-9]

High TMB[10]
(check radiation-assoc, some OS, CS, AS, MPNST)

Non-Responders:[11]

- Most LMS
- Most visceral AS
- Bone sarcomas
- Clear cell sarcoma
- GIST
- Myxoid LPS
- Synovial sarcomas
- Pediatric sarcomas

- BUT only 20% of these super-responder subtypes will actually get durable benefit (except ASPS, cutaneous angiosarcomas)
- Lack of “foreign-ness” prevents generation of tumor-specific immune cells to be reactivated by immunotherapy

Florou…Wilky et al, JITC 2019

1. Tawbi et al, Lancet Oncol 2017, 2. Burgess et al, ASCO 2019, 3. D’Angelo et al Lancet Oncol 2018, 4. Chen et al, ASCO 2020, 5. Somaiah et al, Lancet Oncol 2022, 6. Blay et al, Lancet Oncol 2023, 7. Chen et al, NEJM 2023, 8. Wagner et al, JITC 2021, 9. D’Angelo et al, Nat Commun 2022, 10. Cancer Genome Atlas Research Network, Cell 2017, 11. Wood et al, ASCO Ed Book, 2024.

Selected PD1/PD-L1 combination trials in sarcomas

CTLA-4
Macrophages
Microenvironment
Chemo

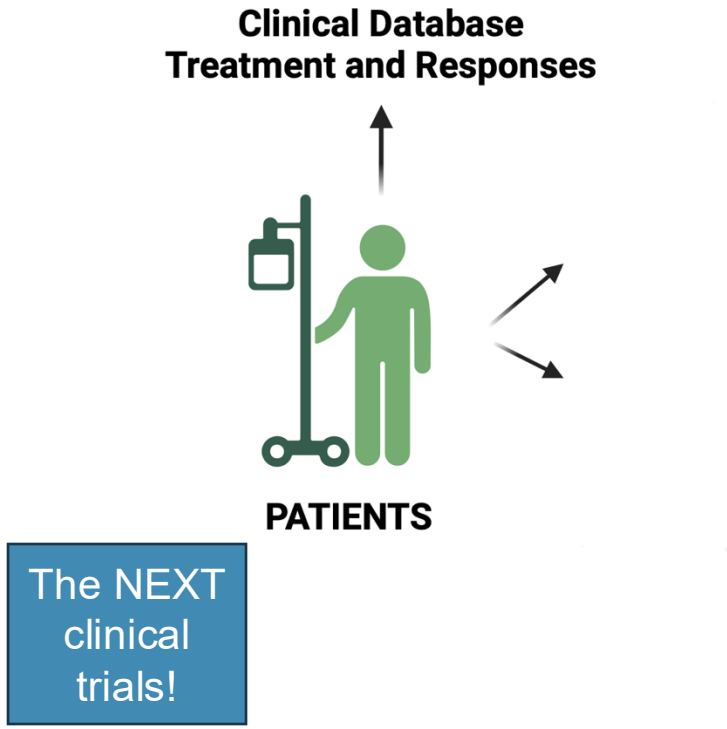
Study Agents	ORR	mPFS	Subtypes (RR)
Pembrolizumab[1]	18%	4.5 mo	UPS 23%[2], LPS 10%
Ipilimumab/Nivo[3,4]	16%	4.1 mo	UPS 28.6%[4], LPS 14.3%
Cyclophosphamide/Pembro[5]	2%	1.4 mo	1 PR mSFT
Axitinib/Pembro[6]	25%	4.7 mo	Non-ASPS 9.5%, ASPS 54.5%
Doxorubicin/Pembro[7,8]	22 – 36.7%	5.7-7.8 mo	LMS 30%, UPS 66%, LPS 40%
Sunitinib/Nivo[9]	9.3%	5.9 mo	PRs in AS, ESMC, SS, ASPS
Trabectedin/Ipi/Nivo[10] (Ph II)	22%	6.7 mo	UPS, SS, LPS, LMS
Durvalumab/Tremelimumab[11]	12%	2.8 mo	chordoma 20%, AS and UPS (20% ea)
Gem/Doce/Retifanlimab[12]	17-50%	PFS_{6mo} 44-60%	LMS, UPS, LPS, AS, MFS
Cabozantinib/Ipi/Nivo[13]	11%	5.4 mo	MFS, AS, LMS, ES
Trabectedin/nivolumab[14]	3-12%	2.6 mo (B), 5.5 mo (A)	LMS/LPS (A) other (B)

SS: synovial sarcoma, UPS: undifferentiated pleomorphic sarcoma, LPS: liposarcoma, uLMS: uterine leiomyosarcoma, mSFT: malignant solitary fibrous tumor, ASPS: alveolar soft part sarcoma, AS: angiosarcoma, ESMC: extraskeletal myxoid chondrosarcoma, ES: epithelioid sarcoma, MFS: Myxofibrosarcoma

1. Tawbi et al, Lancet Oncol 2017. 2. Burgess et al ASCO 2019. 3. D'Angelo et al, Lancet Oncol 2018. 4. Chen et al, ASCO 2020. 5. Toulmonde et al, JAMA Oncol, 2018. 6. Wilky et al, Lancet Oncol 2019. 7. Pollack et al, JAMA Oncol 2020. 8. Livingston et al, CCR, 2021. 9. Martin-Broto et al, ESMO 2019 10. Chawla et al, ASCO 2019 11. Somaiah et al, Lancet Oncol 2022 12. Rosenbaum et al, ASCO 2022. 13. Van Tine et al, ASCO 2023. 14. Reichardt et al, ASCO 2023.

Sarcoma Principles: Think bedside to bench and back again.

- We need to learn from every patient with every tumor on every trial.



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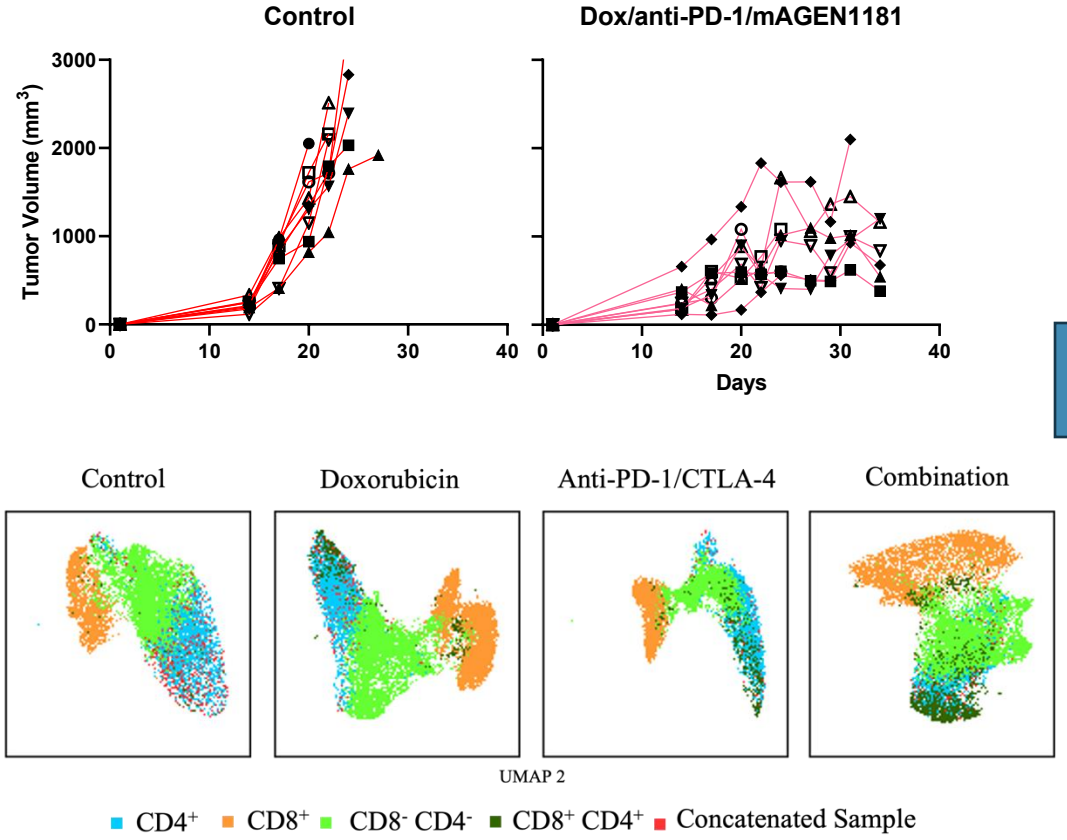
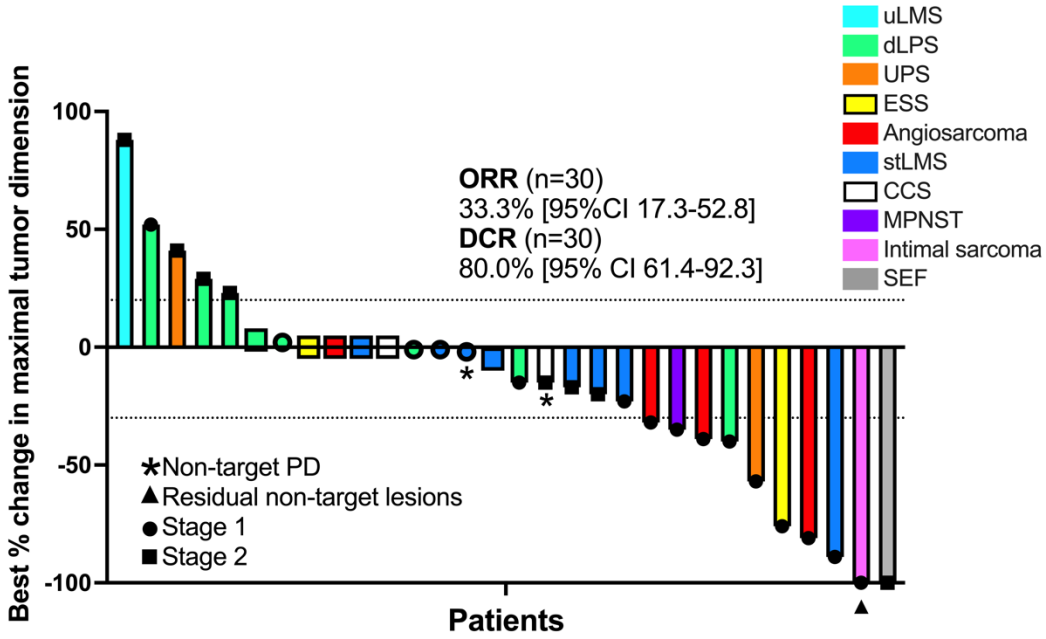
Doxorubicin plus dual immunotherapy for sarcoma

MICE



PATIENTS!



Analysis of tumor and blood samples for markers of response and resistance

Wilky et al, In press Clin Cancer Res

Summary and conclusions

- **Rare tumors like sarcomas need new therapies as much as the more common cancers… arguably even more! We are lightyears behind!!!**
- **Requires creativity, resourcefulness, collaborative spirit, efficiency and resilience**
- **THINK BIG… but also think small…**
  - WISH – pool data from across the globe, REALITY – learn from every patient (even if it's a small number)

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Maureen Mida, MS
Sumra Chaudhry, BS (Post-Bacc Scholar)
Jeff Rytlewski, MD (Heme-Onc fellow)
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Davila Lab:

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Joseph Magno, PhD Candidate
Pearl Wilcock, PhD Candidate
Liz Franks Widoff, PhD

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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

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