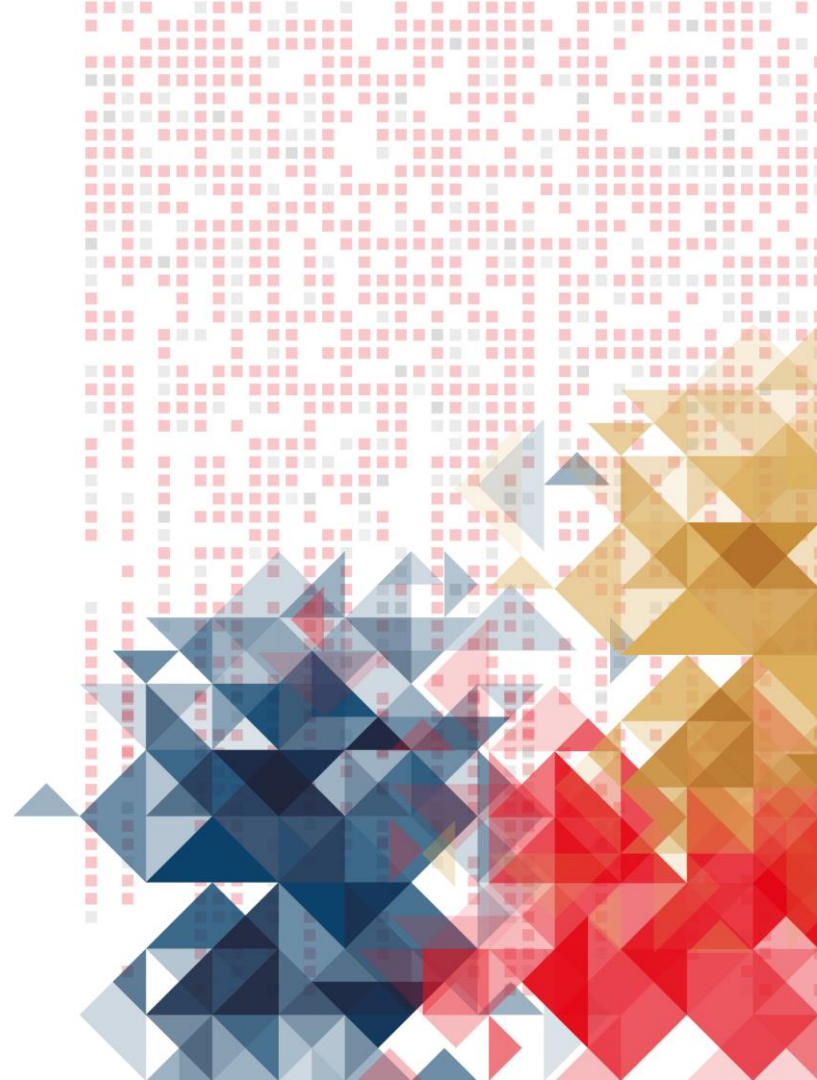


PD-1 checkpoint inhibitors in sarcoma: Evidence and future indications

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Sarcoma Medical Oncology
Early Drug Development
Cellular Therapeutics Core
Memorial Sloan Kettering Cancer Center



DECLARATION OF INTERESTS

Sandra D'Angelo

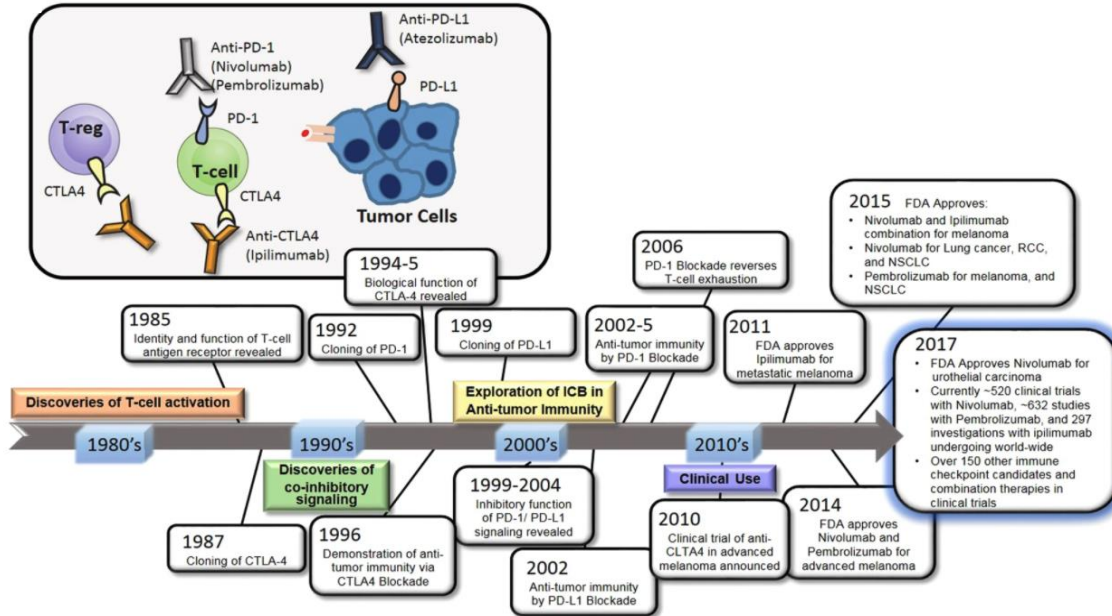
Commercial Interest(s)	Nature of Relationship
Amgen, EMD Serono, GlaxoSmithKline, Immune design, Adaptimmune, Incyte, Merck, Nektar, Immunocore, Servier	Consulting/Advisory Role/Honorarium
Amgen, BMS, Deciphera, EMD Serono, Incyte, Merck, Nektar	Research Funding
Adaptimmune, EMD Serono, Nektar	Travel, accommodations, expense

Objectives

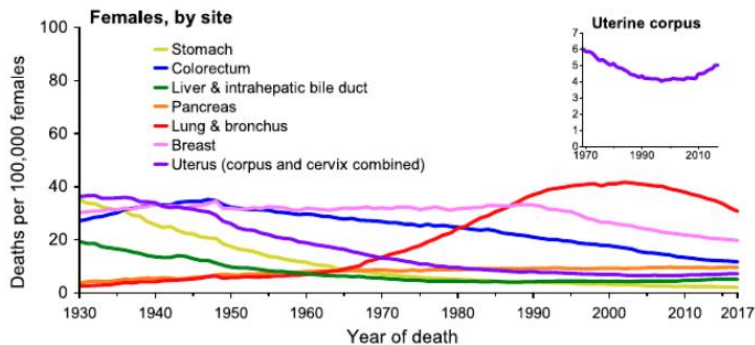
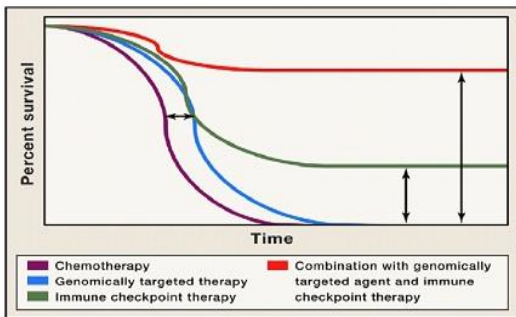
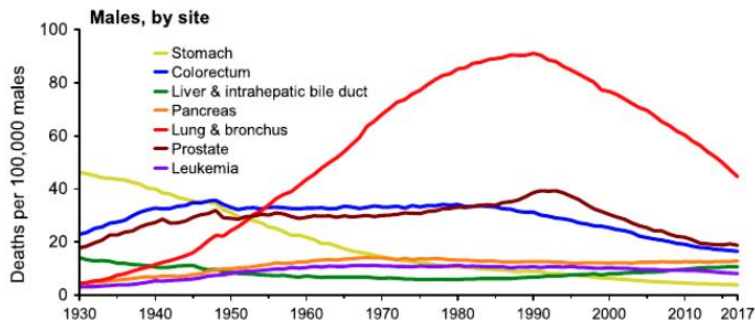
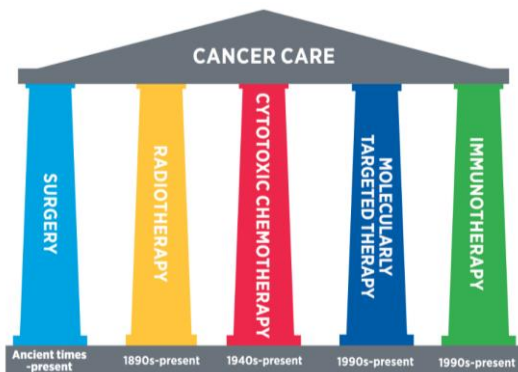
Discuss the role of checkpoint blockade in the treatment of sarcoma

- History
- Challenges
- Success
- Biomarkers
- Future directions

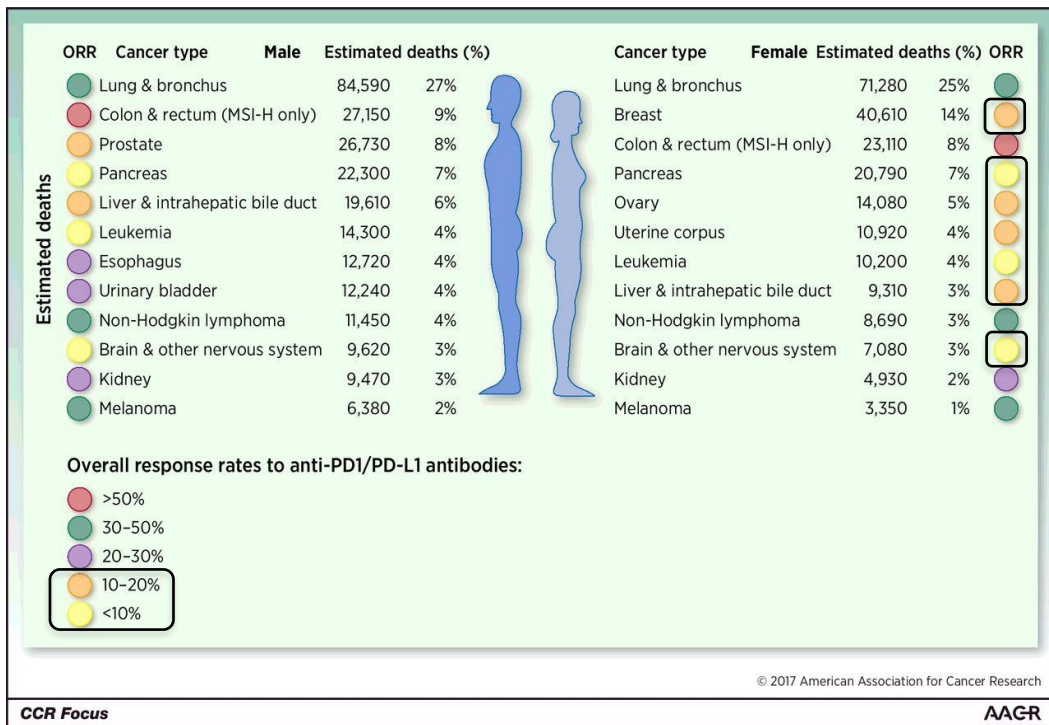
Rapid revolution in immunotherapy field



Unprecedented decrease in mortality

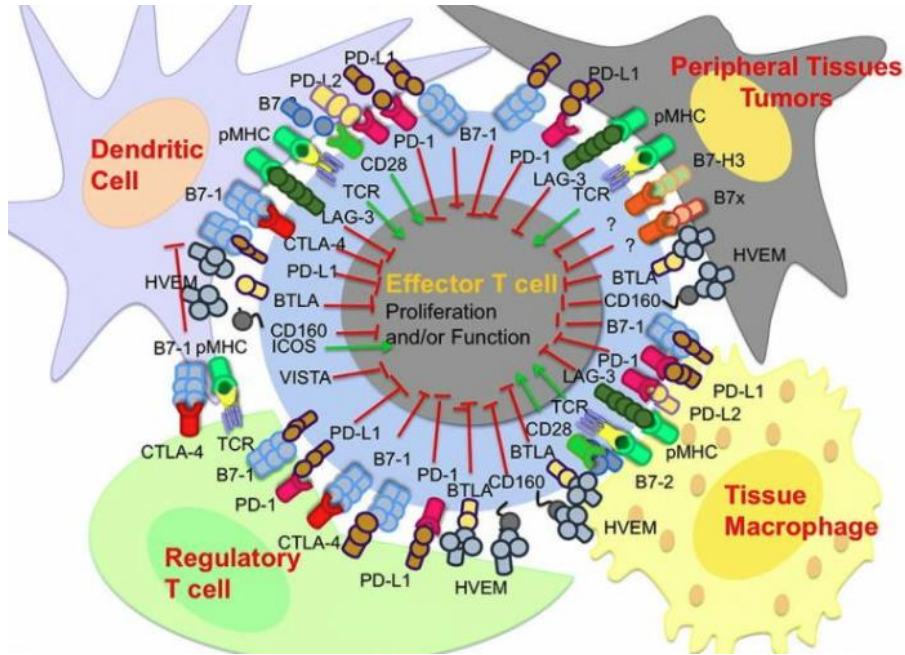


Success of checkpoint blockade

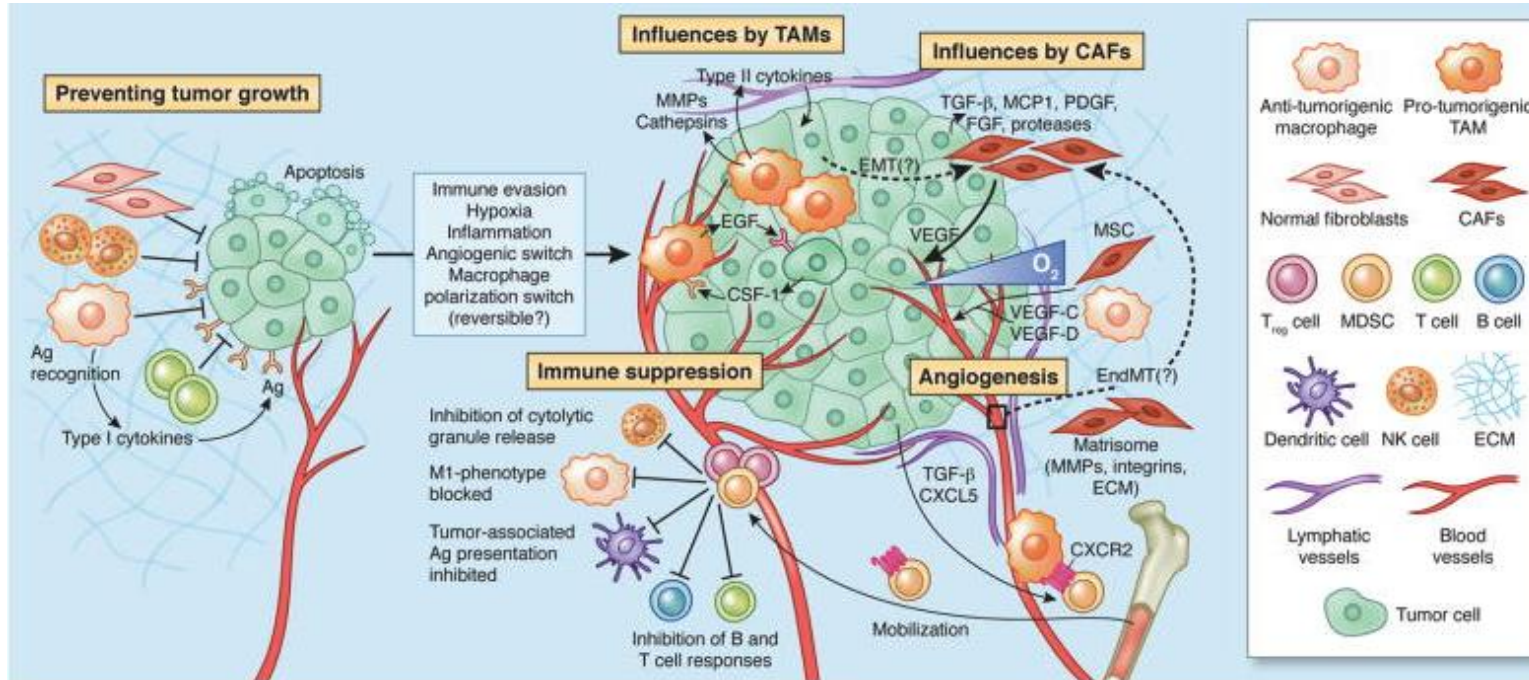


ORR remains in 10-20% range and often not durable

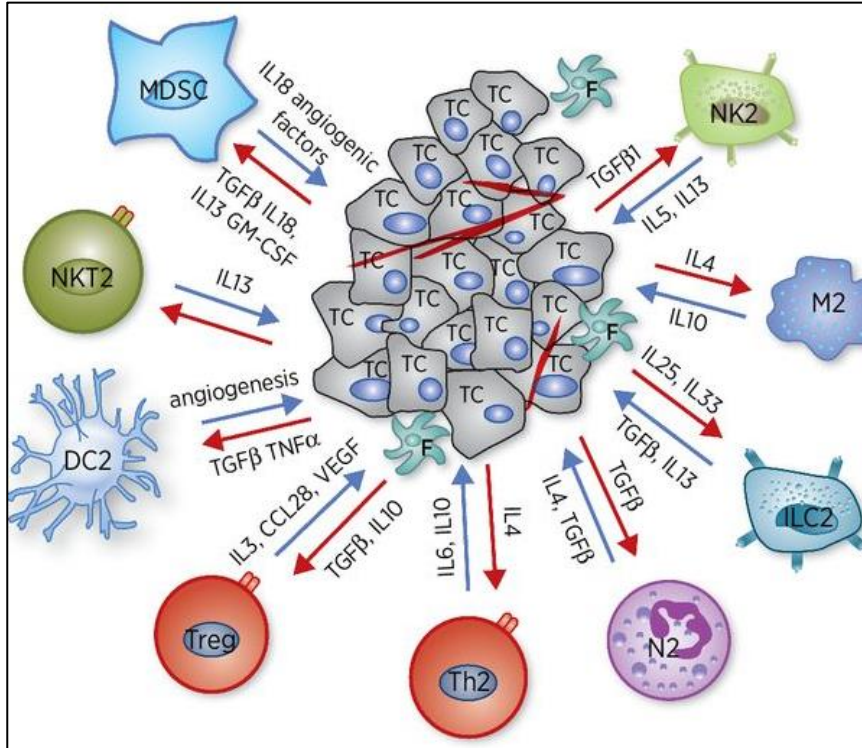
Immunomodulatory pathways are complex



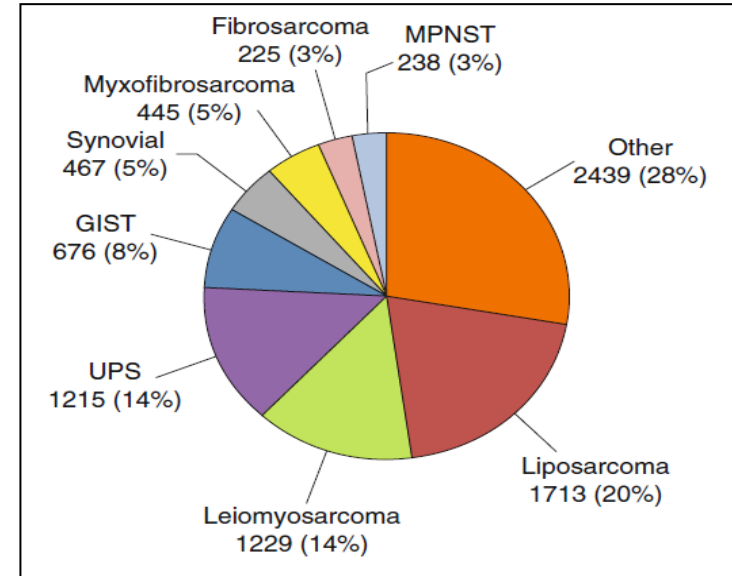
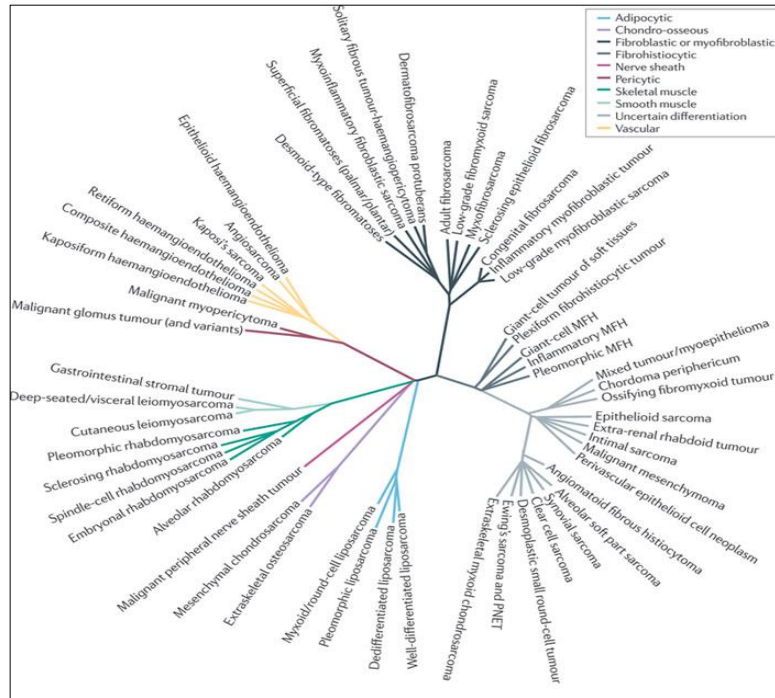
Tumor microenvironment is complex



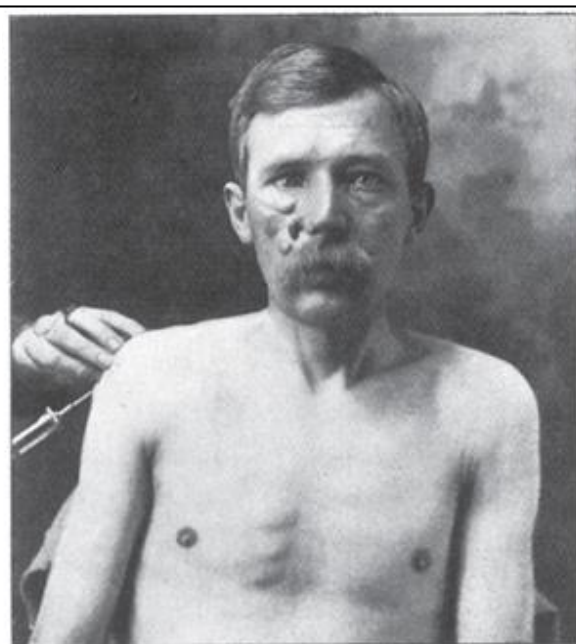
Numerous immunosuppressive signals exist



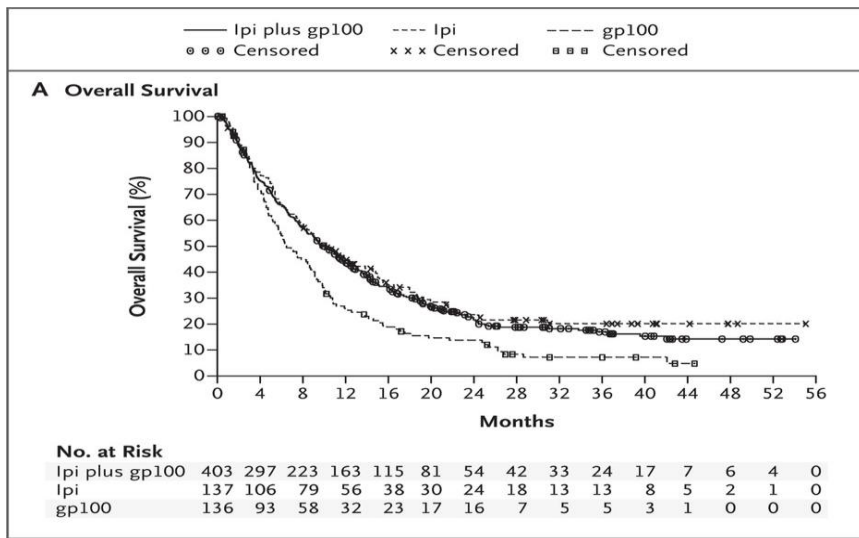
Biggest challenge heterogeneity of sarcoma



Idea of immunotherapy in sarcoma is not new



Ipilimumab initiated modern day immunotherapy



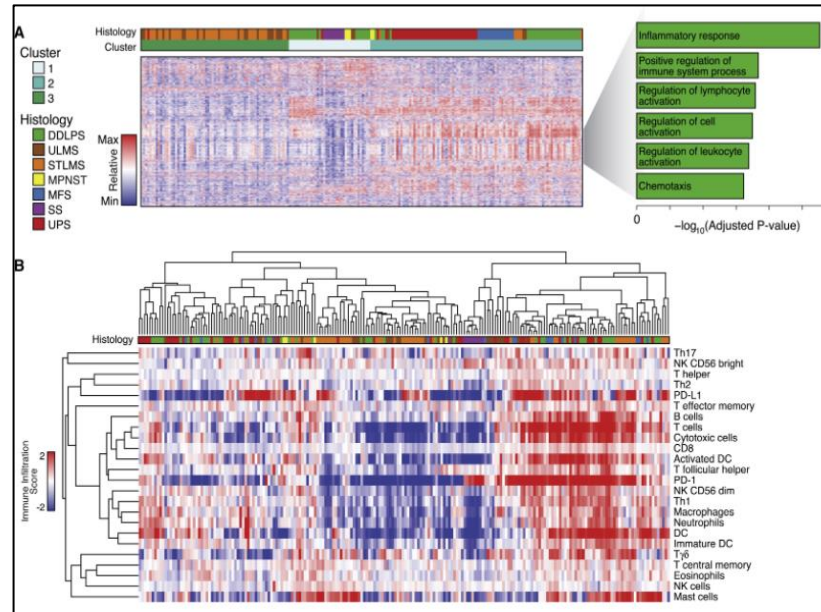
Circa 2005: Ipilimumab in Synovial sarcoma

Age	Gender	NY-ESO-1 immunohistochemistry	HLA-A2	HLA-DP4	Time to progression (months)	Overall survival (months)
43	F	3+	+	+	1.9	3.8
26	F	4+	+	+	0.9	19.7
56	M	3+	+	+	1.9	13.7
32	F	3+	-	+	2.1	3.2
57	F	3+	-	-	0.5	0.8
23	M	2+	+	+	1.8	13.7

Sarcoma TCGA further illustrates variability

UPS/MFS and
DDLPS had the
highest median
macrophage
scores

STLMS had highest
PD-L1 score



Subset of
DDLPS with
immune
signatures of T
cell activation

DDLPS had
highest CD8
score

Sarcoma checkpoint inhibitor studies

Disease	Checkpoint inhibitor	Partner	n	ORR	Median PFS (m)	Author
LMS, UPS, GIST, others	Pembrolizumab	Cyclophosphamide	50	6.70%	1.4	Le Cesne et al
STS	Pembrolizumab	Axitinib	33	25%	4.7	Wilky et al
All Sarcoma	Nivolumab +/- ipilimumab	None	43/42	5%/16%	1.7 /4.1	D'Angelo et al
STS	Pembrolizumab	Cyclophosphamide	57	2%	1.4	Toulmonde et al
All Sarcoma	Pembrolizumab	None	84	18%/5%	4.5/2	Tawbi et al
STS	Ipilimumab	Dasatinib	28	0%	2.8	D'Angelo et al
All Sarcoma	Durvalumab	Tremelimumab	57	14.3%	4.5	Somaiah et al
GIST, UPS, DDLPS	Nivolumab +/- ipilimumab	None	66	0% -14%	1.5 - 5.5	Chen et al
STS	Pembrolizumab	Doxorubicin	30	33%	6.9	Livingston et al
STS	Ipilimumab/Nivolumab	Trabectedin	41	19.50%	6	Gordon et al
STS	Nivolumab	Sunitinib	68	13%	5.6	Martin-Broto
Bone	Nivolumab	Sunitinib	40	5%	3.7	Palmerini et al
STS	Pembrolizumab	Doxorubicin	37	22%	8.1	Pollack et al

ORR consistently < 20% in unselected histologies

ORR <20% with standard chemotherapy

	ORR	OS	PFS
Pazopanib vs placebo *non-adipocytic STS	6% vs 0	12.5m vs 10.7m	4.6m vs 1.6m
Eribulin vs DTIC * LPS/LMS	4% vs 5%	13.5m vs 11.5m	2.6m vs 2.6m
Trabectin vs DTIC *LPS/LMS	9.9% vs 6.9%	12.4m vs 12.9m	4.2m vs 1.5m
Dox olara vs dox *STS	18% vs 12%	26.m vs 14.7m	4.1m vs 6.6m
Gem doce vs gem*STS	16% vs 8%	18m vs 11.5m	6.2m vs 3m

What is the impact of trial design?
Lack of signal? Lack of efficacy ?

Recent sarcoma successes have been in histology specific studies



Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial

William D Tap, Hans Gelderblom, Emanuela Palmerini, Jayesh Desai, Sebastian Bauer, Jean-Yves Blay, Thierry Alcindor, Kristen Ganjoo, Javier Martin-Broto, Christopher W Ryan, David M Thomas, Charles Peterfy, John H Healey, Michiel van de Sande, Heather L Gelhorn, Dale E Shuster, Qiang Wang, Antoine Yver, Henry H Hsu, Paul S Lin, Sandra Tong-Starkens, Silvia Stacchiotti*, Andrew J Wagner*, on behalf of the ENLIVEN investigators†

ABI-009 (*nab-sirolimus*) in Advanced Malignant Perivascular Epithelioid Cell Tumors (PEComa): Preliminary Efficacy, Safety, and Mutational Status from AMPECT, an Open-label Phase 2 Registration Trial

Andrew J. Wagner, MD, PhD,¹ Vinod Ravi, MD,² Kristen N. Ganjoo, MD,³ Brian A. Van Tine, MD,⁴ Richard F. Riedel, MD,⁵ Rashmi Chugh, MD,⁶ Lee D. Cramer, MD, PhD,⁷ E. Maria Gordon, MD,⁸ Jason L. Hornick, MD, PhD,⁹ David J. Kwiatkowski, MD, PhD,⁹ Heng Du, MD,² Berta Grigorian,¹⁰ Anita N. Schmid, PhD,¹⁰ Shihe Hou, PhD,¹⁰ Katherine Harris, DrPH,¹⁰ Neil Desai, PhD,¹⁰ Mark A. Dickson, MD¹¹

Tazemetostat in advanced epithelioid sarcoma with loss of INI1/SMARCB1: an international, open-label, phase 2 basket study



Mrinal Gounder, Patrick Schöffski, Robin L Jones, Mark Agulnik, Gregory M Cote, Victor M Villalobos, Steven Attia, Rashmi Chugh, Tom Wei-Wu Chen, Thierry Jahan, Elizabeth T Loggers, Abha Gupta, Antoine Italiano, George D Demetri, Ravin Ratan, Lara E Davis, Olivier Mir, Palma Dileo, Brian A Van Tine, Joseph G Pressey, Trupti Lingaraj, Anand Rajarethinam, Laura Sierra, Shefali Agarwal, Silvia Stacchiotti

ORIGINAL ARTICLE

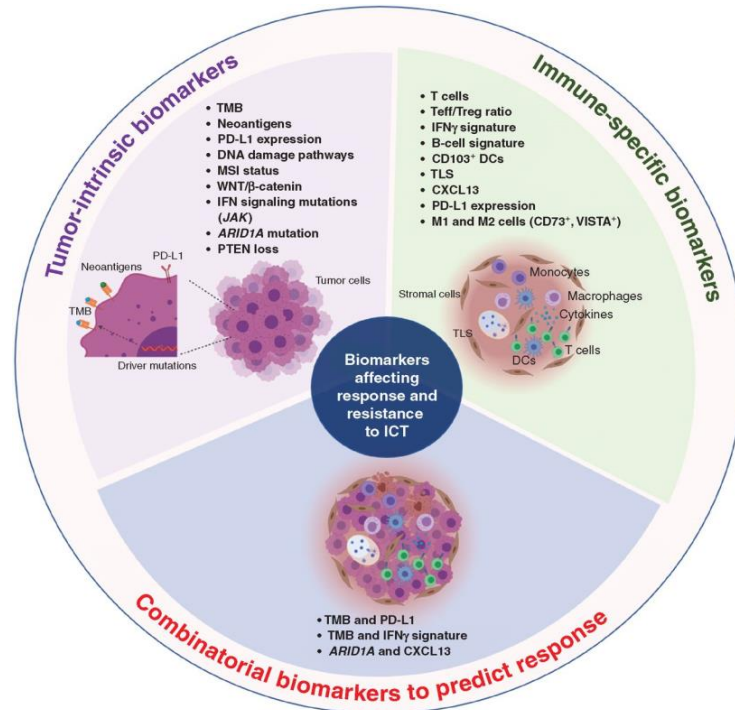
Sorafenib for Advanced and Refractory Desmoid Tumors

Mrinal M. Gounder, M.D., Michelle R. Mahoney, M.S., Brian A. Van Tine, M.D., Ph.D., Vinod Ravi, M.D., Steven Attia, D.O., Hari A. Deshpande, M.D., Abha A. Gupta, M.D., Mohammed M. Milhem, M.D., Robert M. Conry, M.D., Sujana Movva, M.D., Michael J. Pishvaian, M.D., Ph.D., Richard F. Riedel, M.D., Tarek Sabagh, M.D., William D. Tap, M.D., Natally Horvat, M.D., Ethan Basch, M.D., Lawrence H. Schwartz, M.D., Robert G. Maki, M.D., Ph.D., Narasimhan P. Agaram, M.B., B.S., Robert A. Lefkowitz, M.D., Yousef Mazaheri, Ph.D., Rikiya Yamashita, M.D., Ph.D., John J. Wright, M.D., Ph.D., Amylou C. Dueck, Ph.D., and Gary K. Schwartz, M.D.

Sorting/splitting may tease out efficacy (or lack of)

Histology	Drugs	Response rate
UPS	Pembrolizumab	23%
	Nivolumab + ipilimumab	29%
ASPS	Atezolizumab	42%
	Pembrolizumab + axitinib	55%
Angiosarcoma	CTLA4 blockade, pembrolizumab, pembrolizumab + axitinib	71%
DDLPS	Pembrolizumab	10%
	Nivolumab + ipilimumab	14%
Osteosarcoma	Pembrolizumab	4.5%
Uterine LMS	Nivolumab	0%

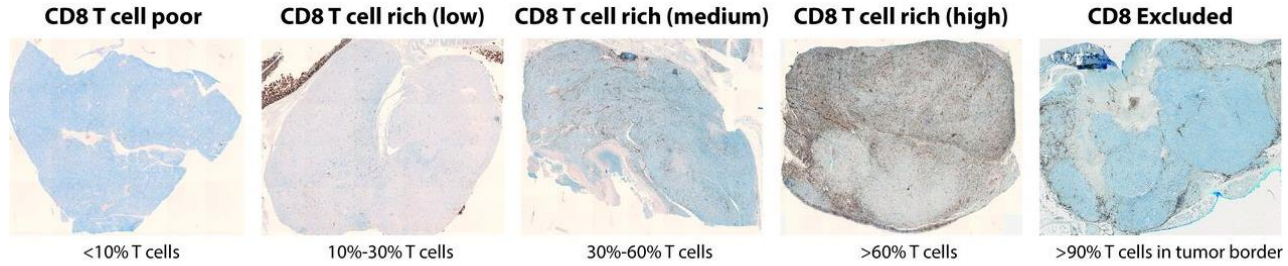
Predictive biomarkers to immunotherapy



IHC-based immune biomarker studies

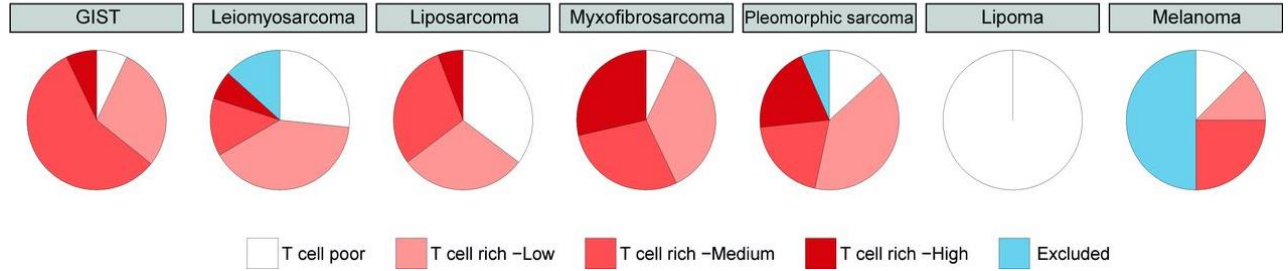
Sarcoma histology	N	CD4+	CD8+	FOXP3+	CD20+	CD163+	PD-1+ TILs	PD-L1+ tumor	Ref.
Soft-tissue sarcoma	105								[57]
	82								[61]
	203								[38]
	33								[31]
Soft-tissue sarcoma with 1+ recurrence	72								[39]
Soft-tissue sarcoma with wide margins	108								[43]
Copy-number driven sarcomas	769								[10]
Alveolar rhabdomyosarcoma	20								[27]
Dedifferentiated liposarcoma	58		**	**					[10,49]
	32								[62]
Desmoplastic small round cell tumor	11		**				**	**	[27]
Embryonal rhabdomyosarcoma	19								[34]
Leiomyosarcoma	17								[33]
Malignant peripheral nerve sheath tumor	76		**	**					[10]
Myxoid liposarcoma	39		**	**					[10]
Osteosarcoma	62								[56]
Retroperitoneal liposarcomas (well-differentiated, dedifferentiated, myxoid/round cell and pleomorphic liposarcoma)	56								[30]
Solitary fibrous tumors	100								[49]
Synovial sarcoma	36								[32]
	22								[27]
Undifferentiated pleomorphic sarcoma	57								[40]
	60								[62]

Differential quantities of immune cells exist



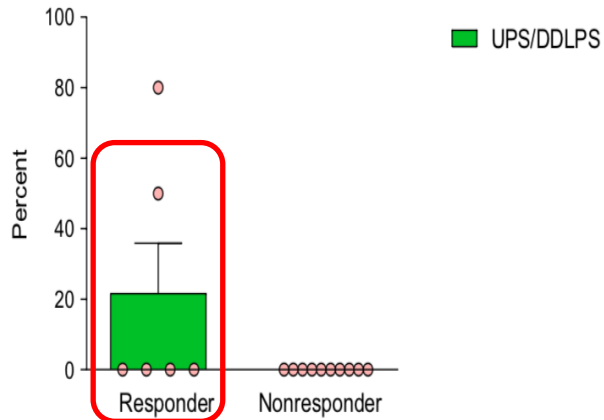
Variation in numbers of CD8+ T cells across STS subtypes

- Highest in GIST and MFH compared to DDLPS

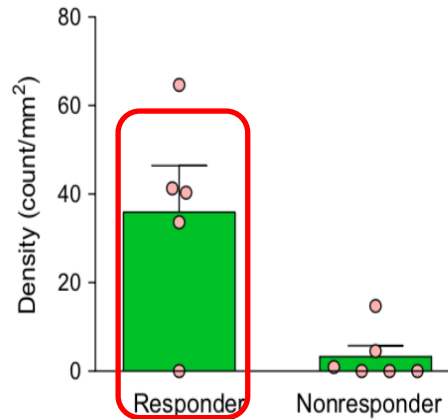


SARC028: Baseline TIL, Tumor infiltrating macrophages and PD-L1 + (UPS/DDLPS) correlate with efficacy

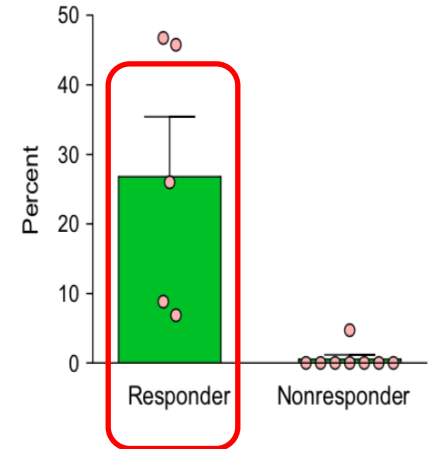
% PD-L1 positive tumor cells



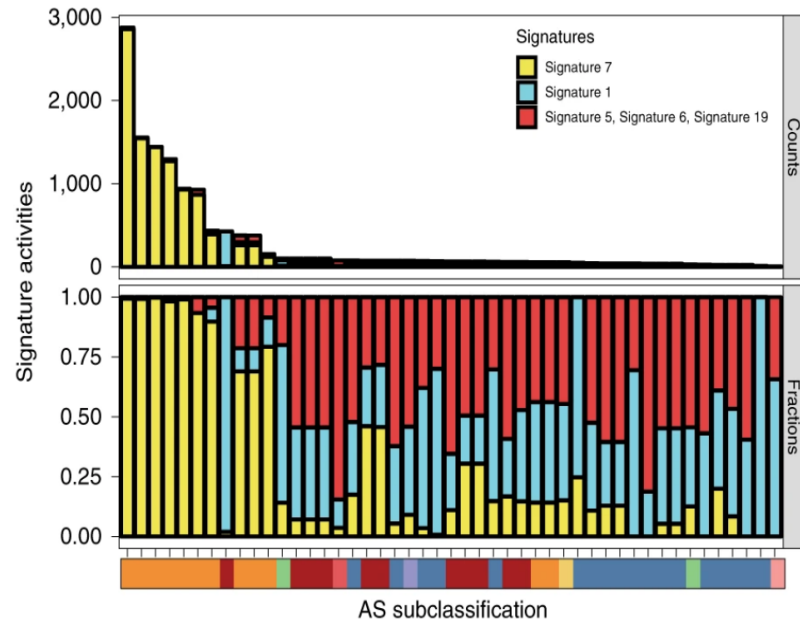
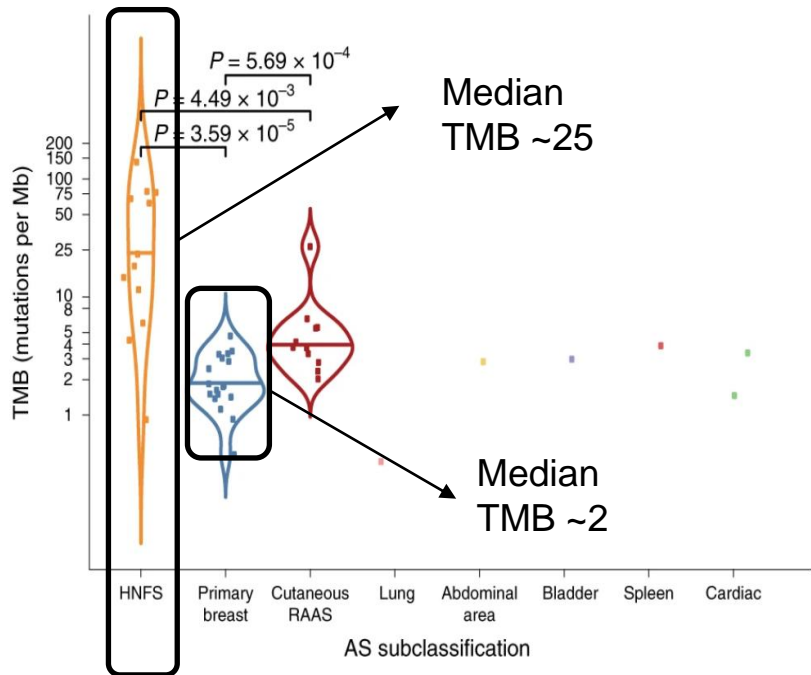
Density of TIL at baseline



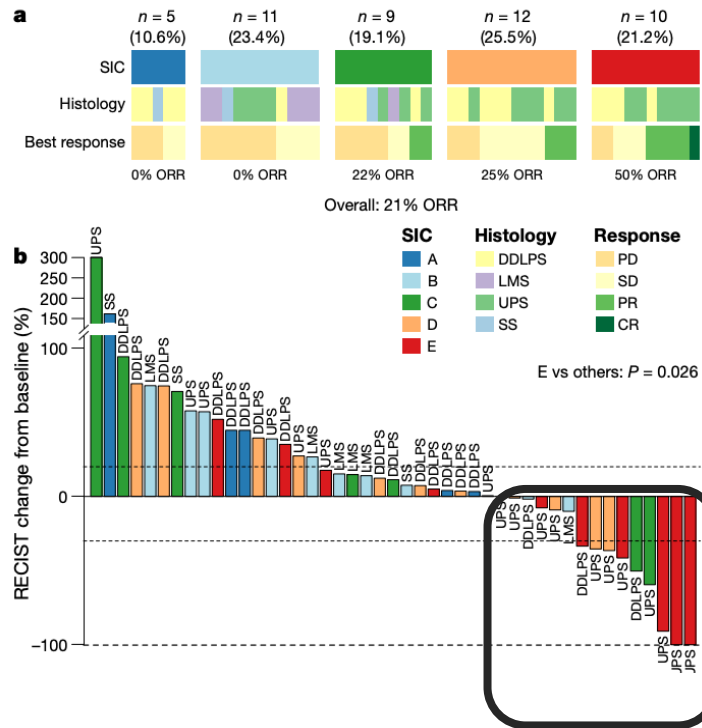
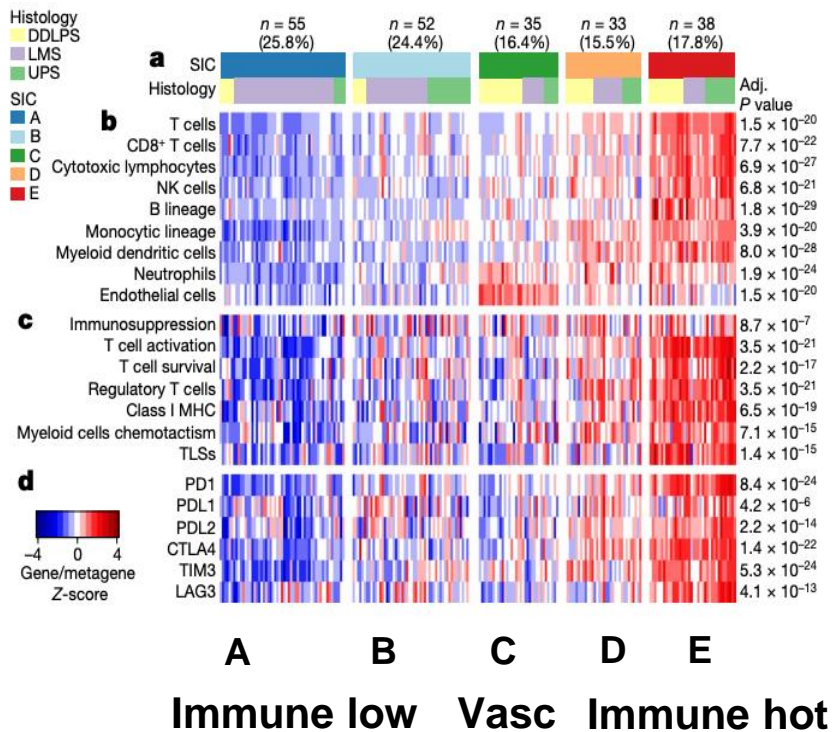
% Tumor infiltrating macrophages at baseline



High TMB/UV signature: Head and neck



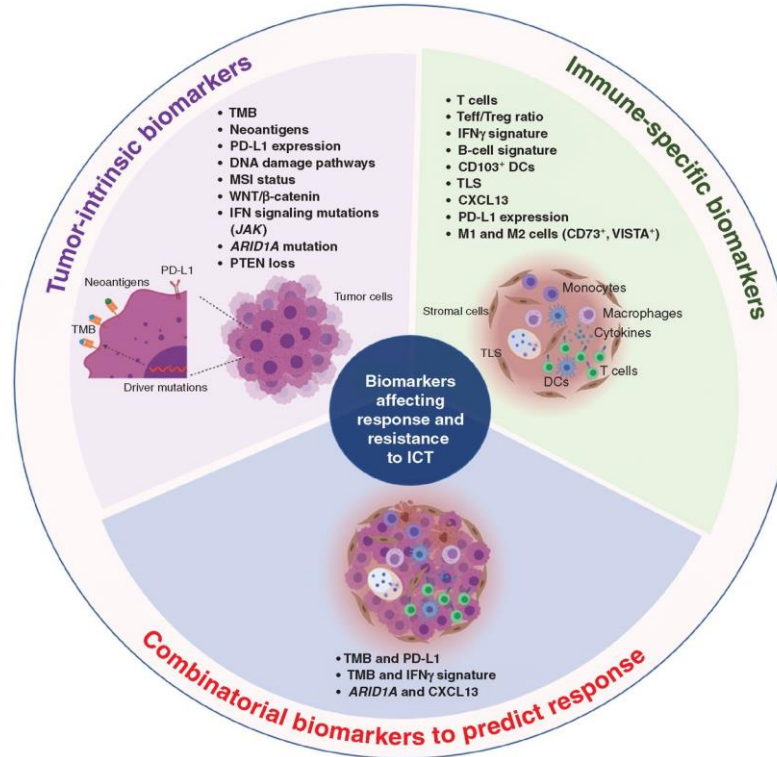
Tertiary lymphoid structures and “hot” tumors



Biomarkers to immunotherapy in Sarcoma

Tumor-intrinsic

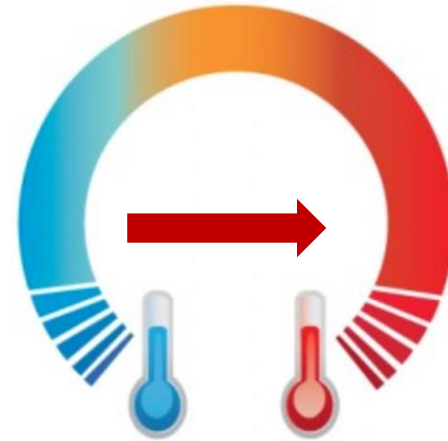
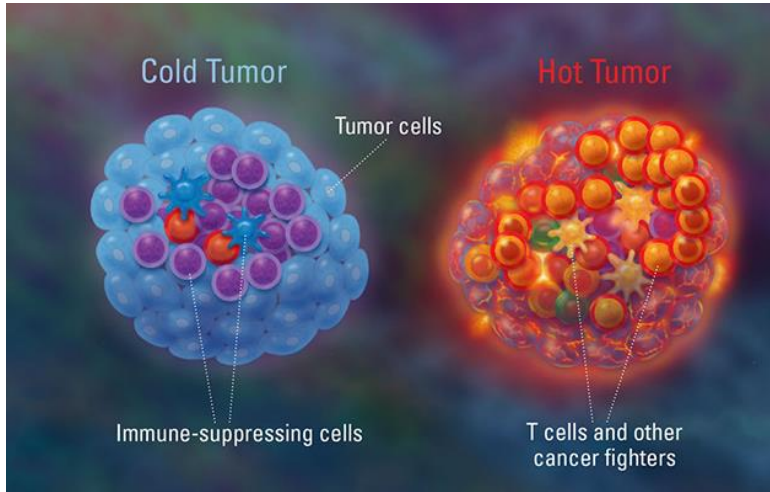
- Low TMB
- Limited neoAg
- 20% LMS DDR
- Variable PDL1 expression
- MSI high uncommon
- Limited PTEN loss



Immune-specific

- Variable T cells
- B cell signature
- IFN signature
- High M2

What is the optimal way to convert tumors and increase immune infiltrates?



Pembrolizumab + TVEC in sarcoma

Variable	RECIST v1.1 (n = 20)	Immune-Related RECIST (n = 20)
Objective response, No. (%)		
Best overall response	7	
Complete response	0	
Partial response	7	
Stable disease	7	
Progressive disease	6 (30)	8 (40)
Best objective response rate, No. (%)	7 (35)	7 (35)
At 24 wk	6 (30)	6 (30)
Disease control rate, No. (%)	14 (70)	12 (60)
Duration of response, No. (%)	7 (35)	7 (35)
mDOR (weeks)	56.1 (49.4-87)	56.1 (49.4-87)

ORR 35%; mDOR – 56.1 weeks
Epithelioid Sarcoma, Cutaneous
Angiosarcoma, UPS, Myxofibrosarcoma,
Sarcoma unclassified

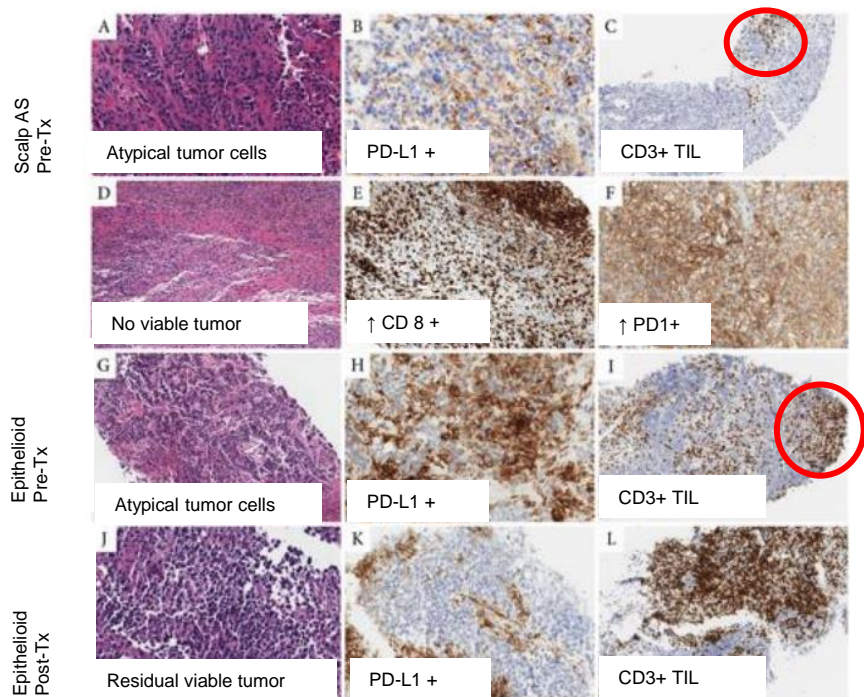


Response Evaluation Criteria In Solid Tumors.



Pembrolizumab + TVEC in sarcoma

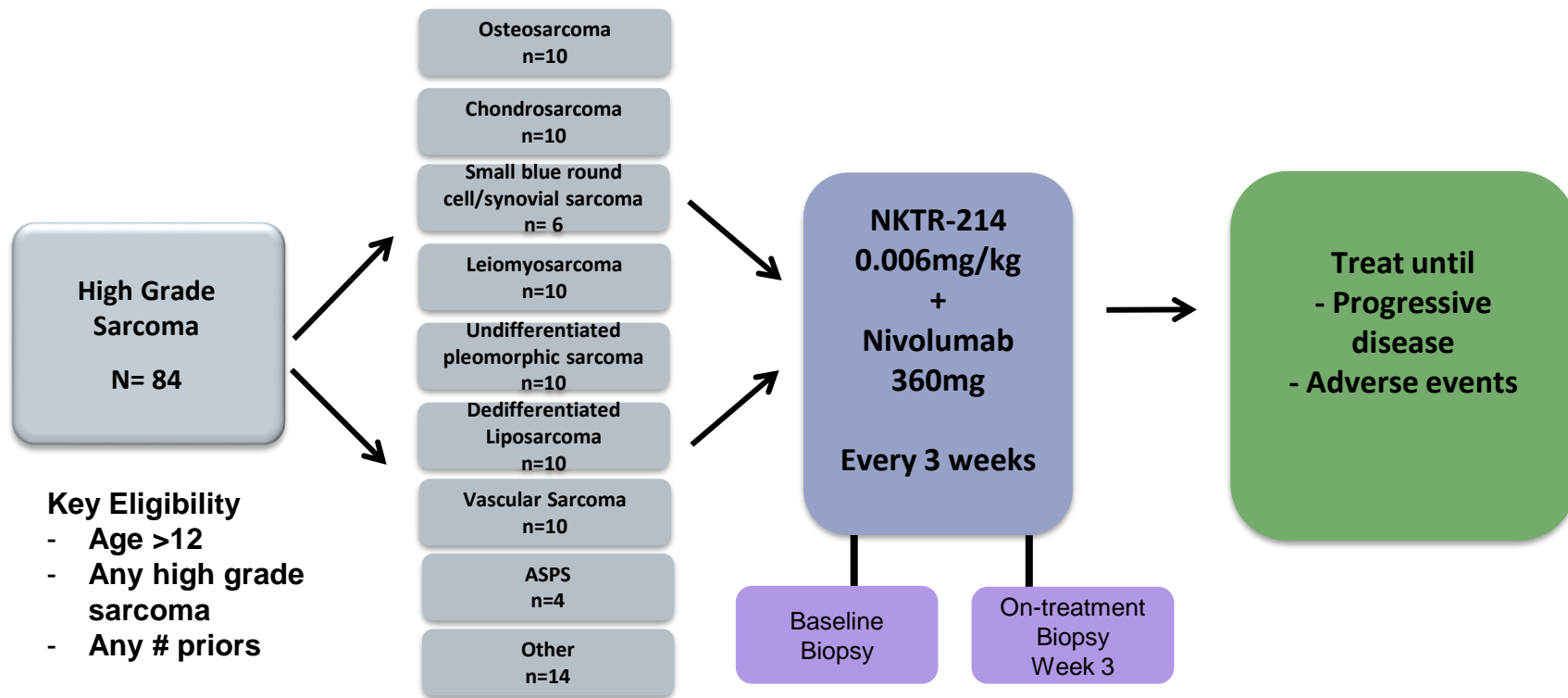
Response: PDL1 expression and TILs at the tumor edge



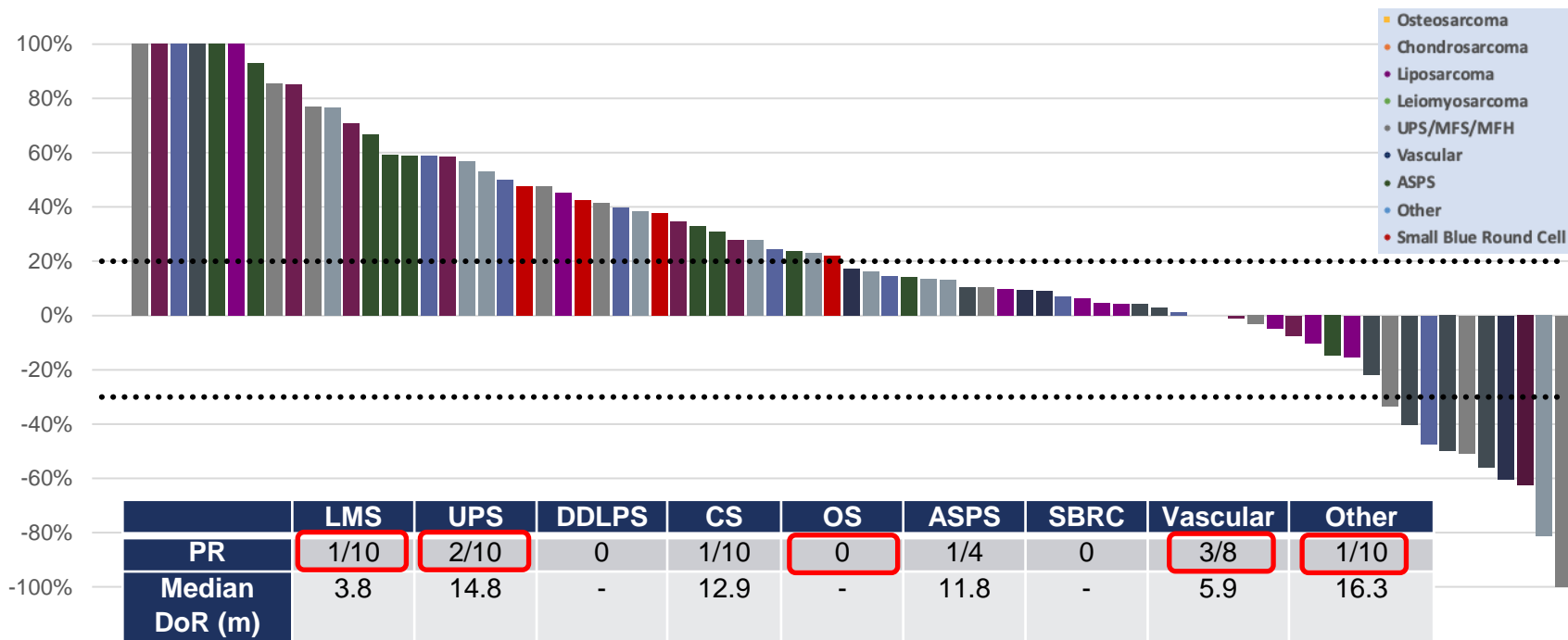
A subset of tumors were “converted” turning from cold to hot

Best Objective Response	PD-L1 status (MPS)(Percent tumor)		TIL Score		Histology
	Pre-Treatment	Post-Treatment	Pre-Treatment	Post-Treatment	
PR	N/A	+ve (10)(5)	N/A	3	UPS
PR	N/A	+ve (60)(75)	N/A	3	UPS
PR	N/A	N/A	N/A	N/A	Myxofibrosarcoma
PR	-ve	+ve (5)(5)	1	3	Angiosarcoma
PR	-ve	+ve (60)(60)	3	3	Angiosarcoma
PR	+ve (15)(15)	N/A	3	N/A	Epithelioid Sarcoma
PR	-ve	N/A	3	N/A	Sarcoma NOS
SD	-ve	+ve (5)(5)	1	3	LMS
SD	-ve	-ve	1	1	ESMC
SD	-ve	-ve	2	1	LMS
SD	-ve	-ve (5)(20)	3	3	LMS
SD	-ve	+ve (90)(65)	2	3	LMS
SD	N/A	+ve (25)(90)	N/A	3	Sarcoma NOS MSI High
SD	-ve	-ve	2	0	ASPS
PD	-ve	N/A	2	N/A	Synovial Sarcoma
PD	-ve	-ve	0	0	Chondrosarcoma
PD	-ve	N/A	3	N/A	Angiosarcoma
PD	-ve	N/A	2	N/A	Sarcoma NOS
PD	-ve	+ve (5)(30)	1	3	MPNST
PD	-ve	-ve	2	3	LMS

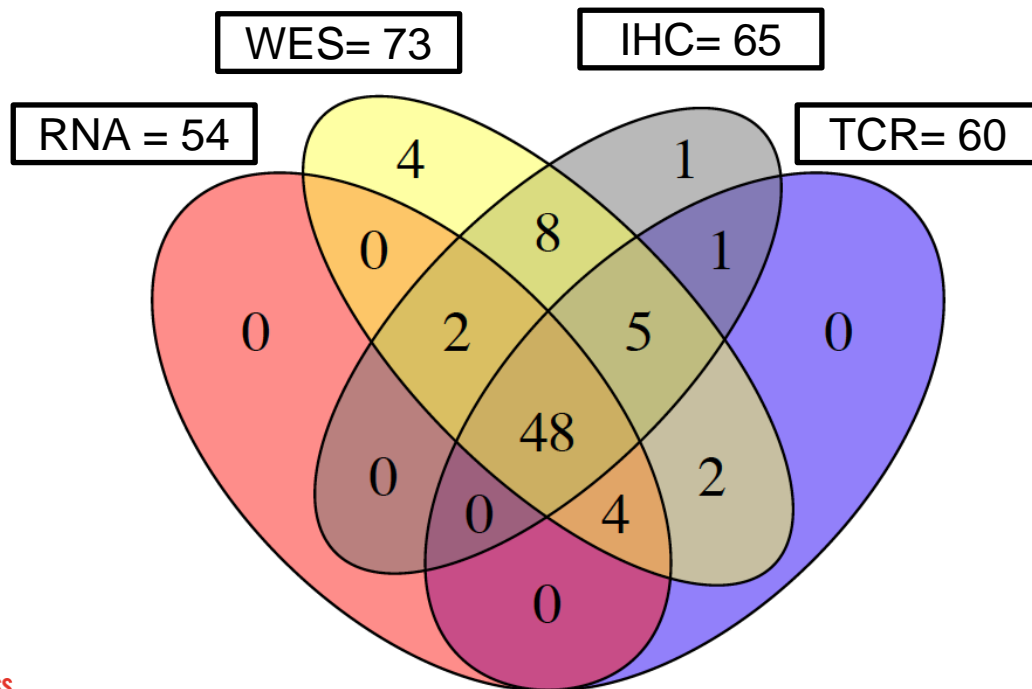
Bempegaldesleukin+ nivolumab in sarcoma



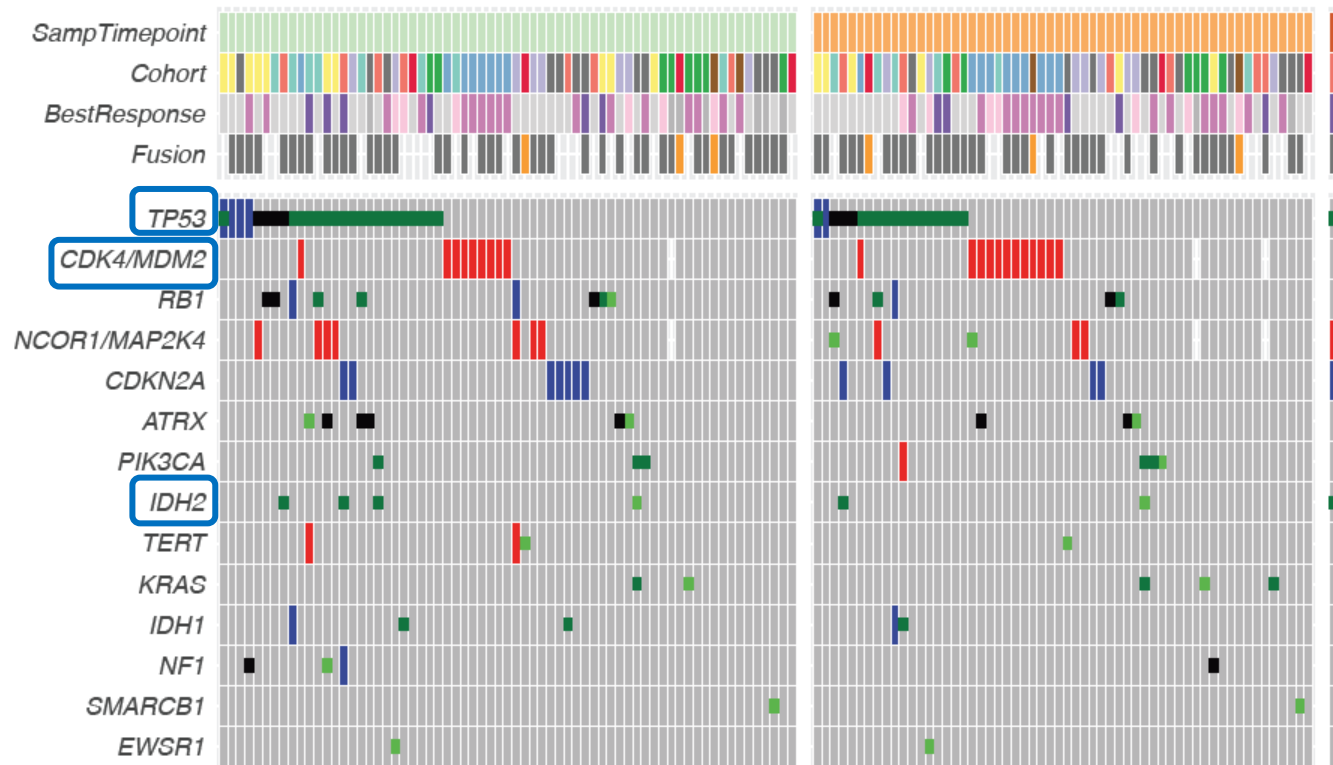
Waterfall plot demonstrates decrease in tumor burden



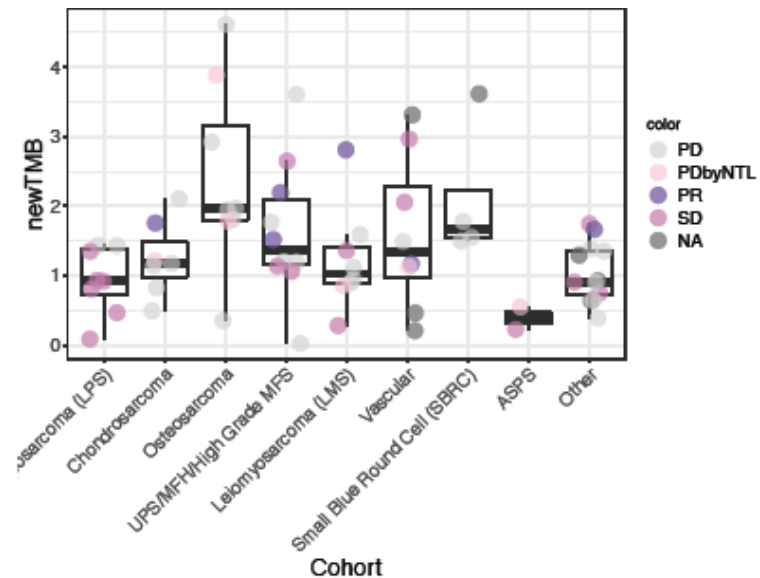
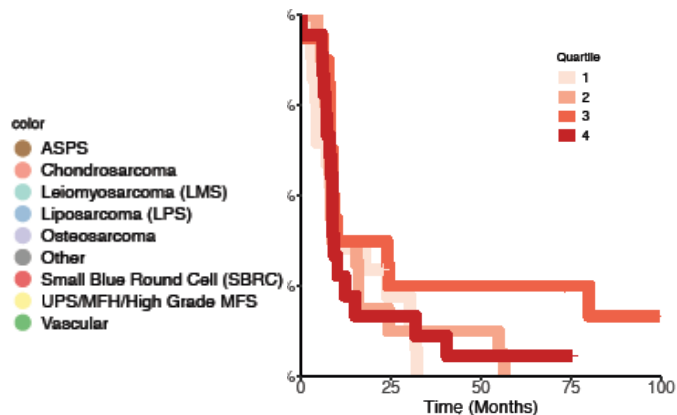
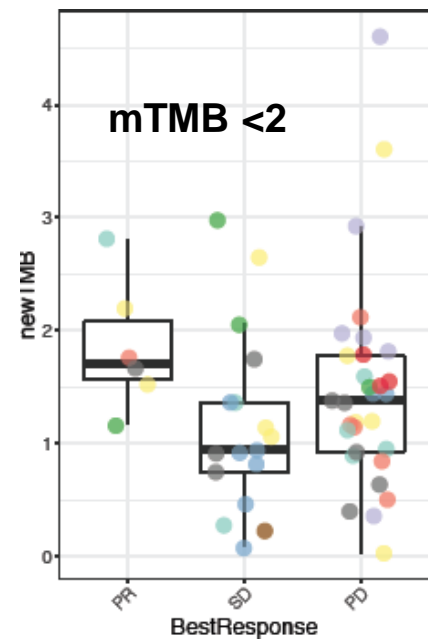
Define the sarcoma IO landscape



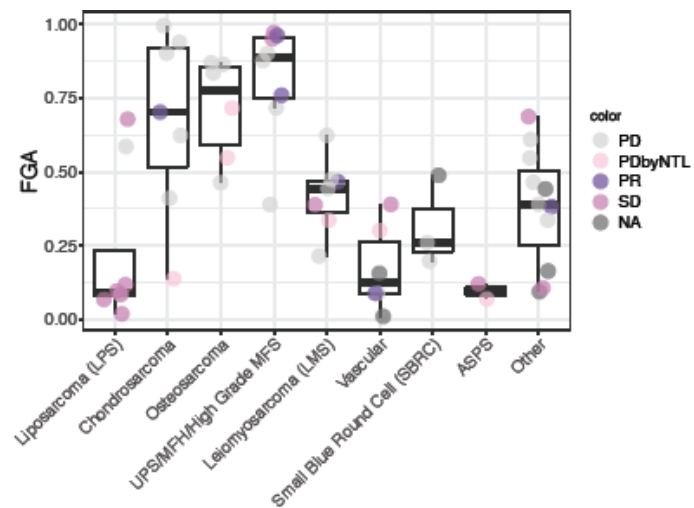
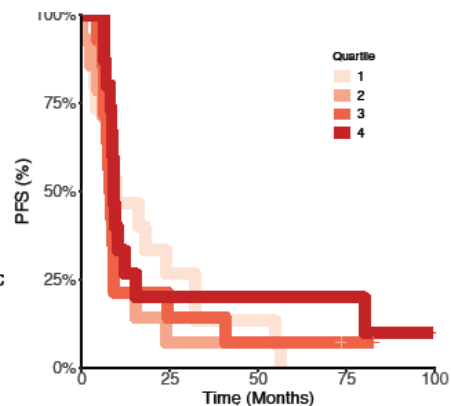
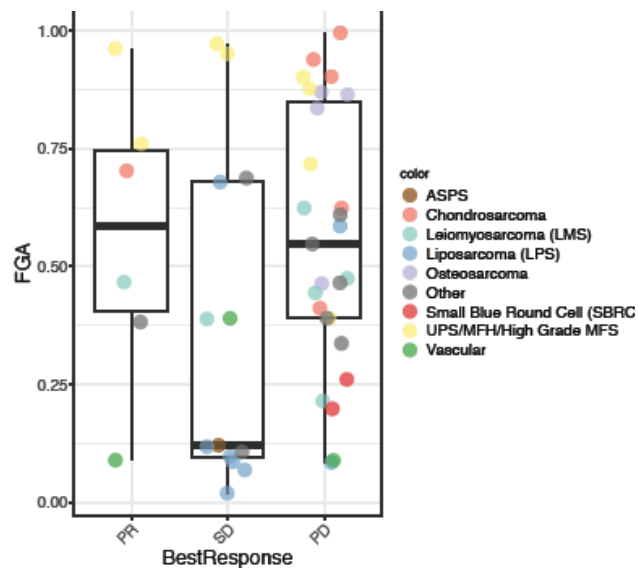
Genomic features of sarcomas



Low TMB which didn't correlate with efficacy

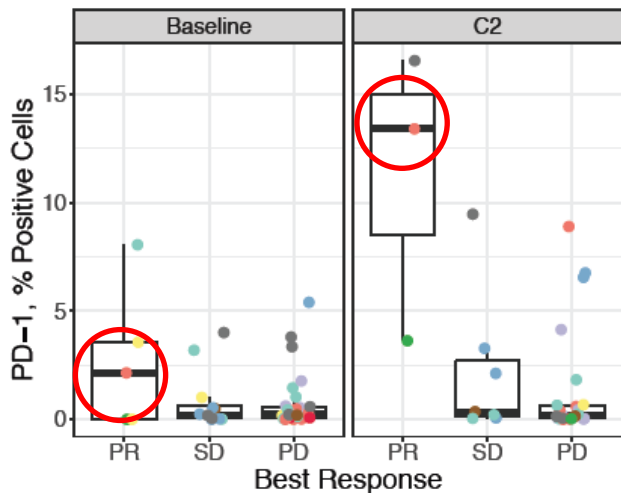


FGA did not correlate with efficacy

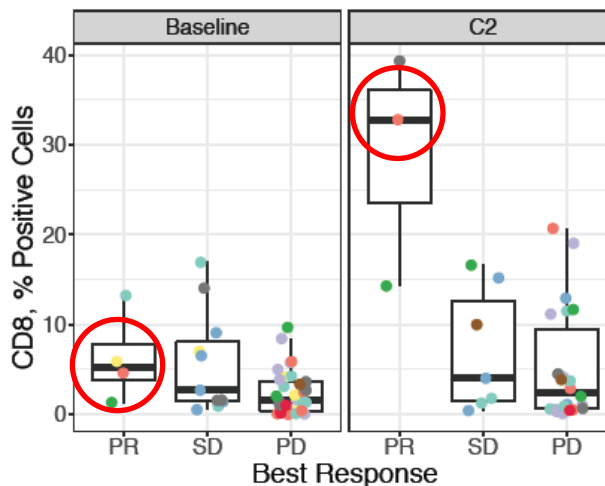


Immune cell populations by IHC

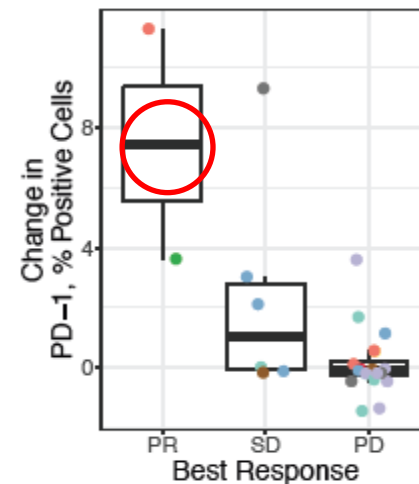
PD-1 expression at baseline and on-treatment associated with ORR



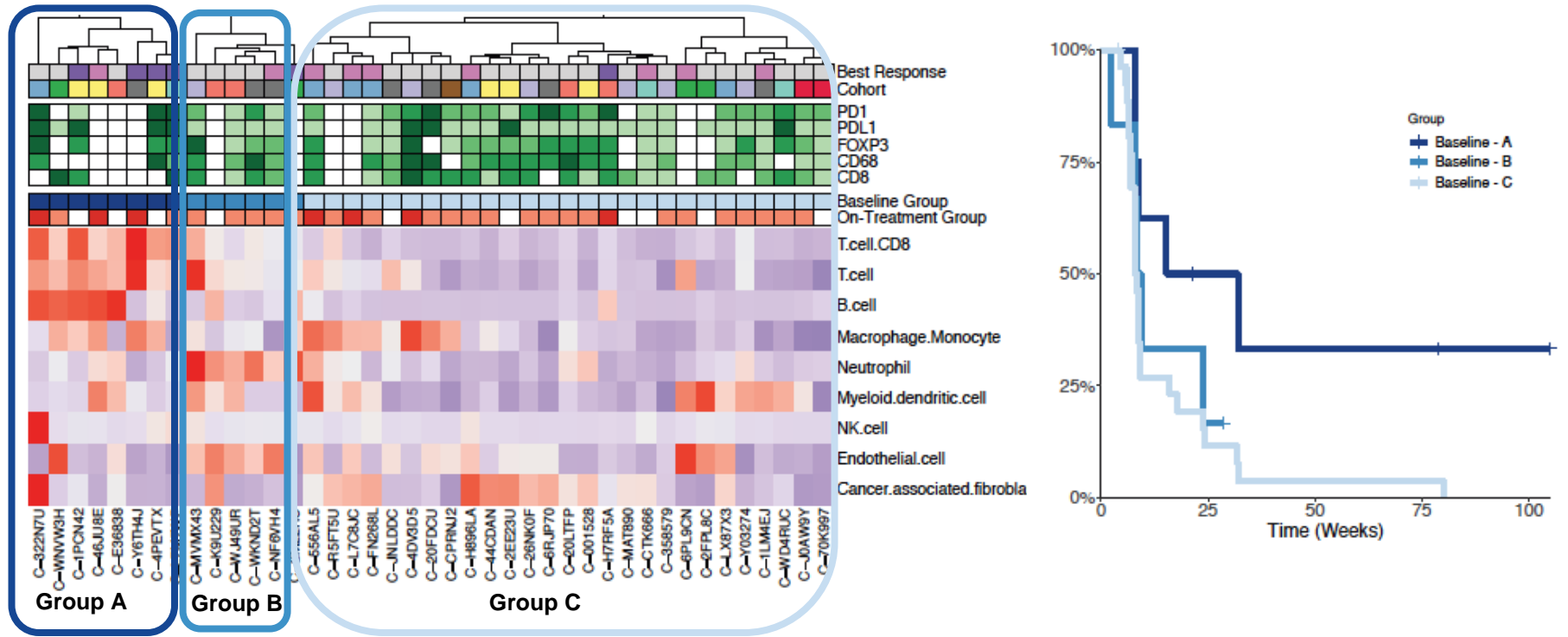
CD8+ T cells on treatment associated with ORR



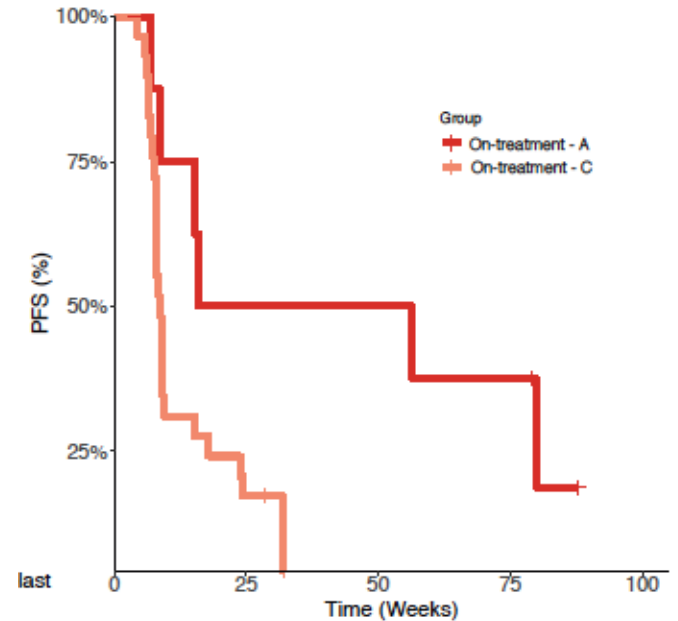
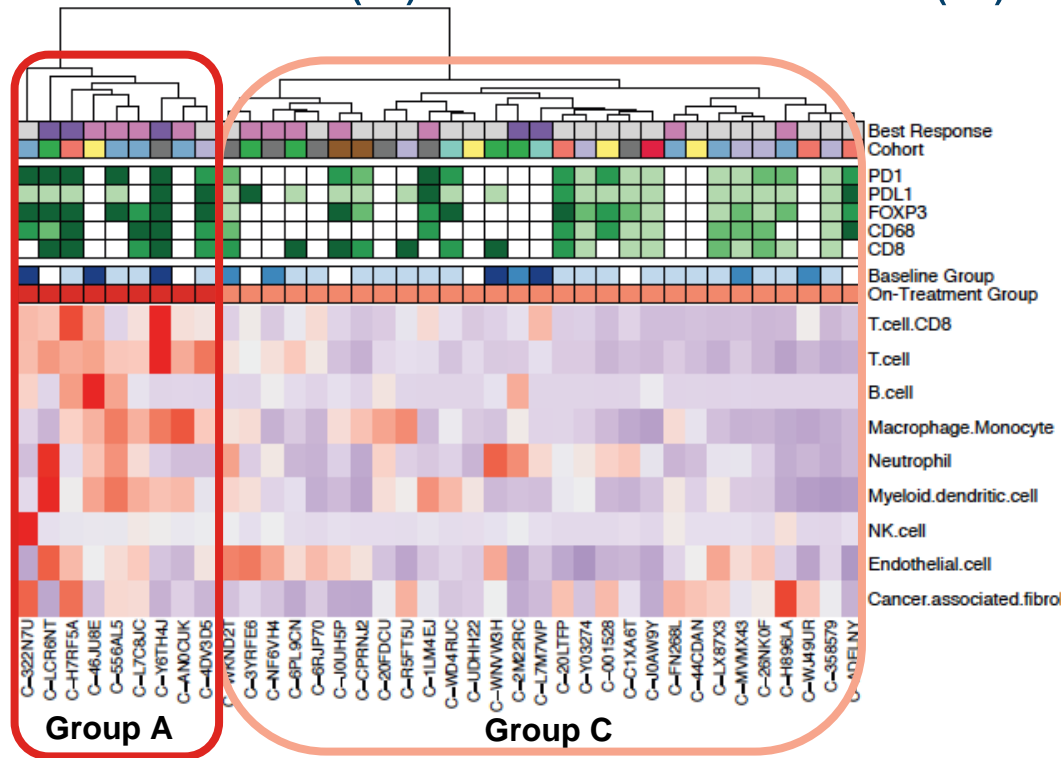
% change in PD-1+ cells



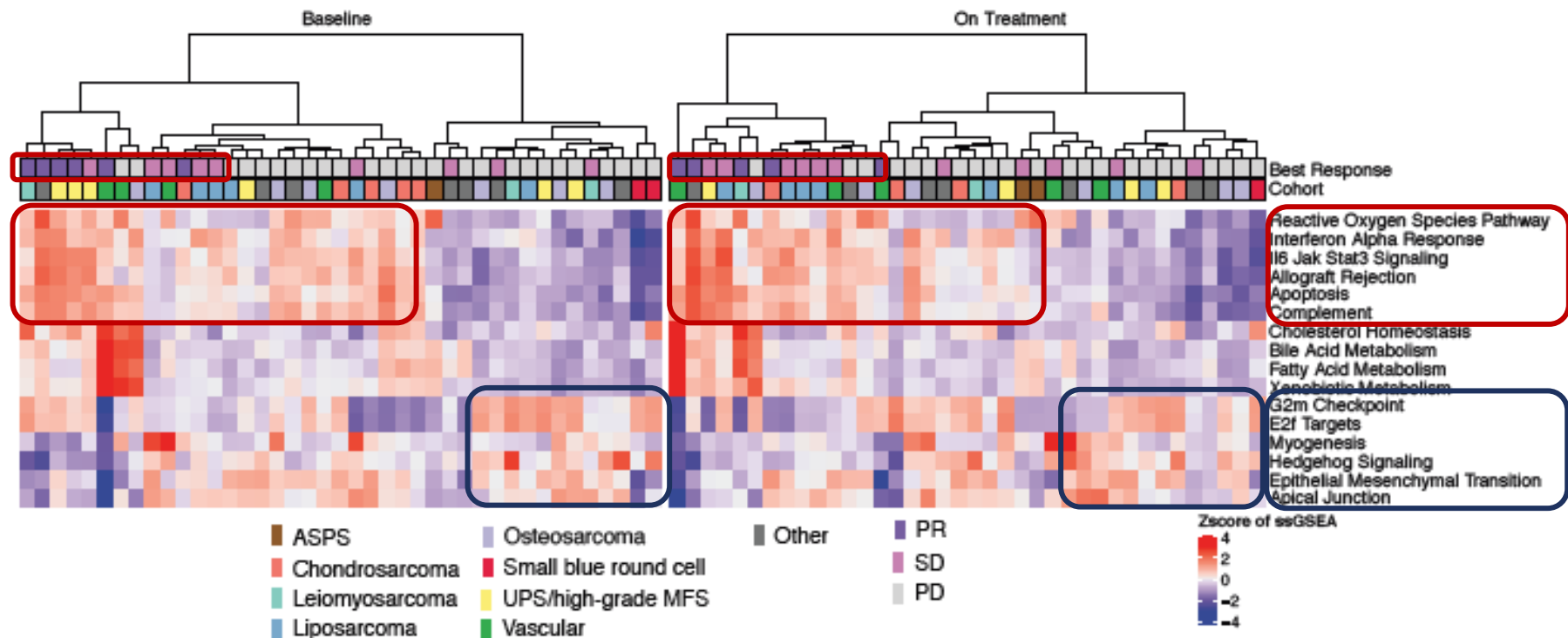
Baseline classification: Immune-hot (A), intermediate (B), Immune cold (C)



On-treatment classification: Immune-hot (A) and immune-cold (C)

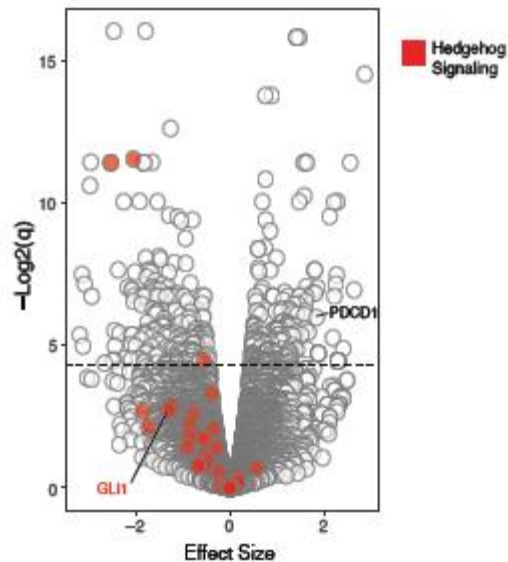


Immune pathways and hedgehog signaling pathways differentiate responses

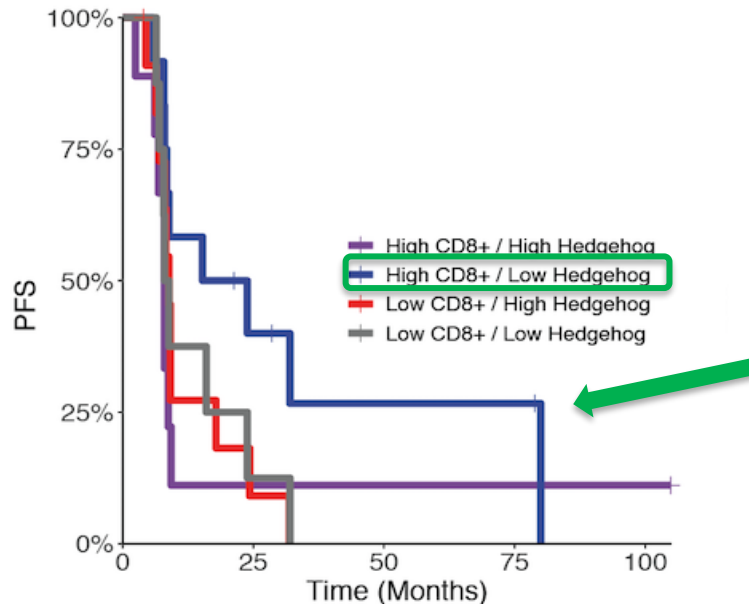


Relevance of hedgehog signaling pathways

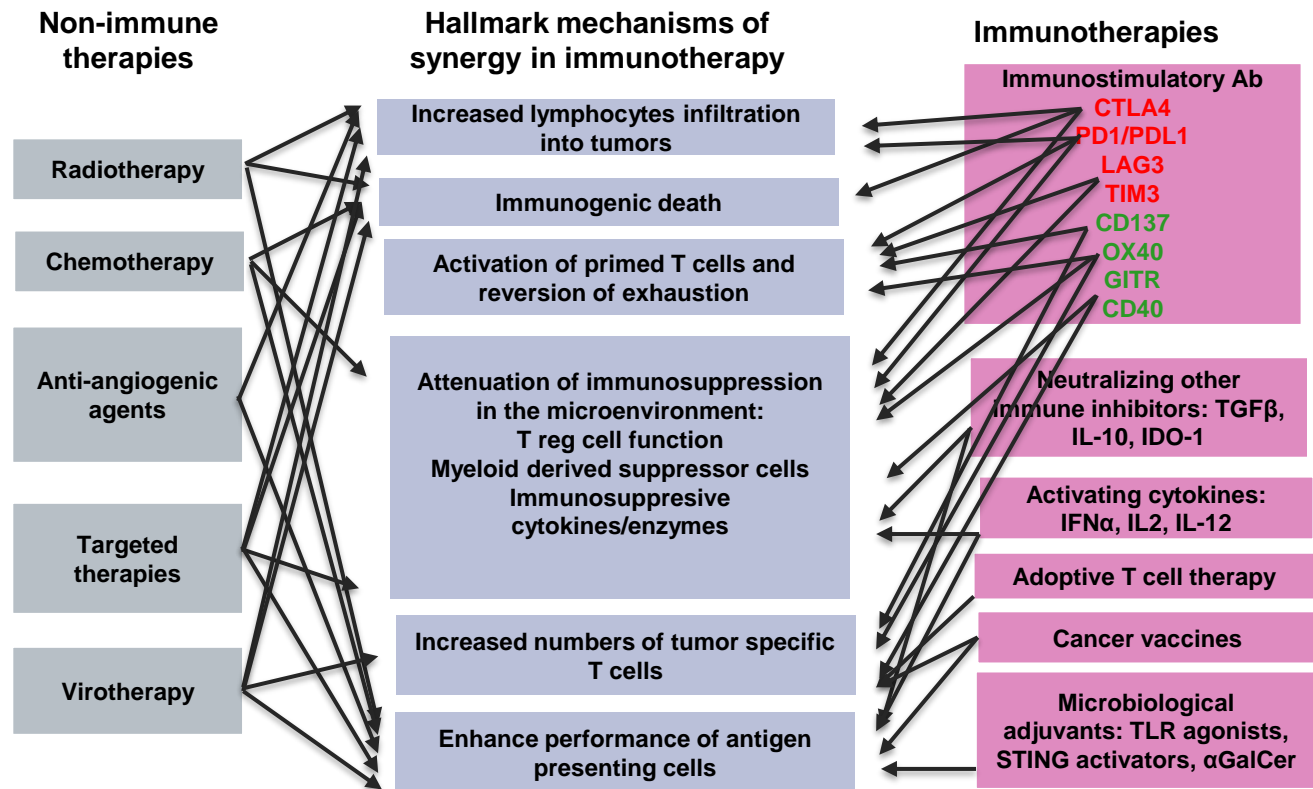
GLI1 was differentially expressed



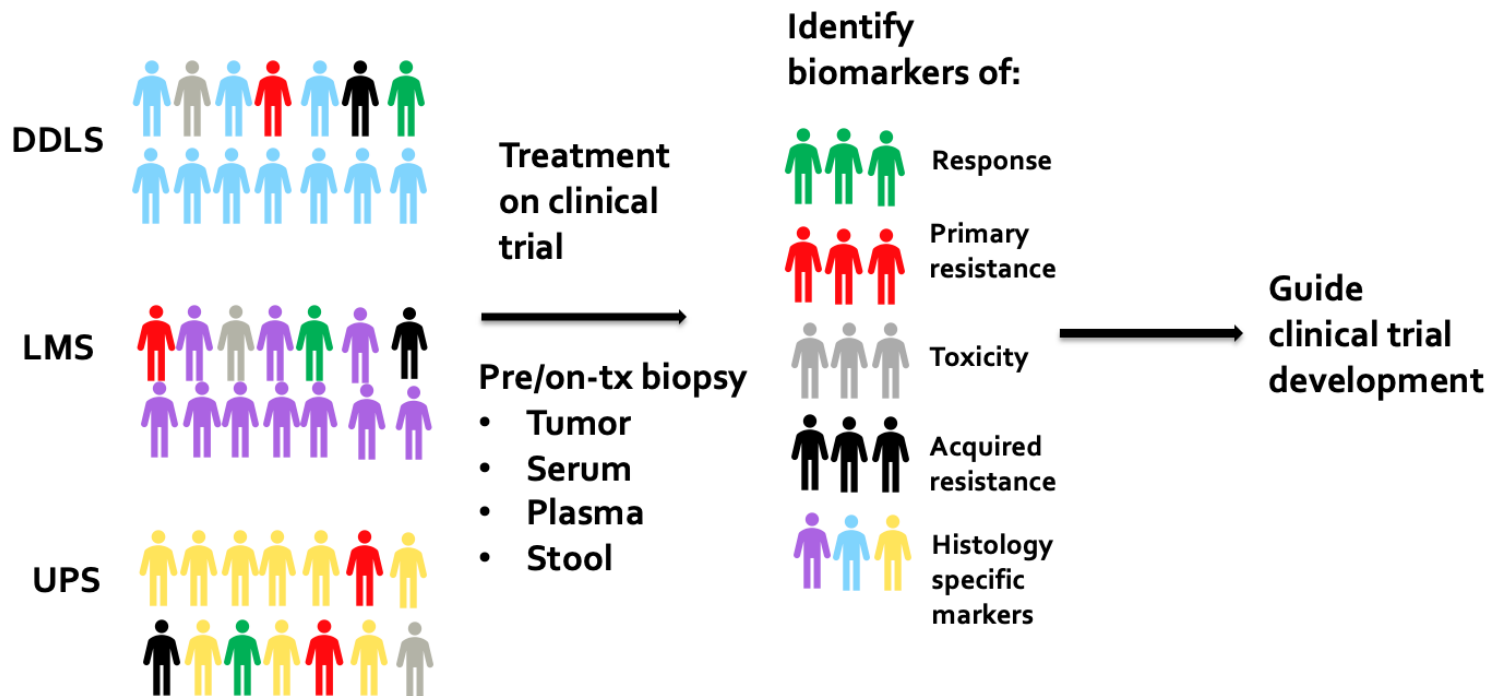
↑ CD8+ T cell & Low Hh gene expression improved PFS



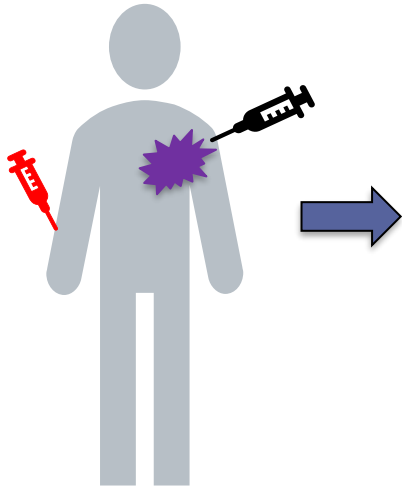
How should we guide future efforts when the options are endless?



Begin with histology specific cohorts and tissue collection



Pre/on-treatment biopsies



Fresh Tumor

- PDX models
- Tumor cell lines

Fresh Frozen

- **Whole exome sequence:** TMB, genomic alterations
- **RNA sequence:** Immune signatures such as T cell activation, antigen presentation, PD1 response, T cell inclusion, macrophages

FFPE

- **Multiplex IHC:** CD3,8, FoxP3, PD1, PDL1, LAG, Tim3,

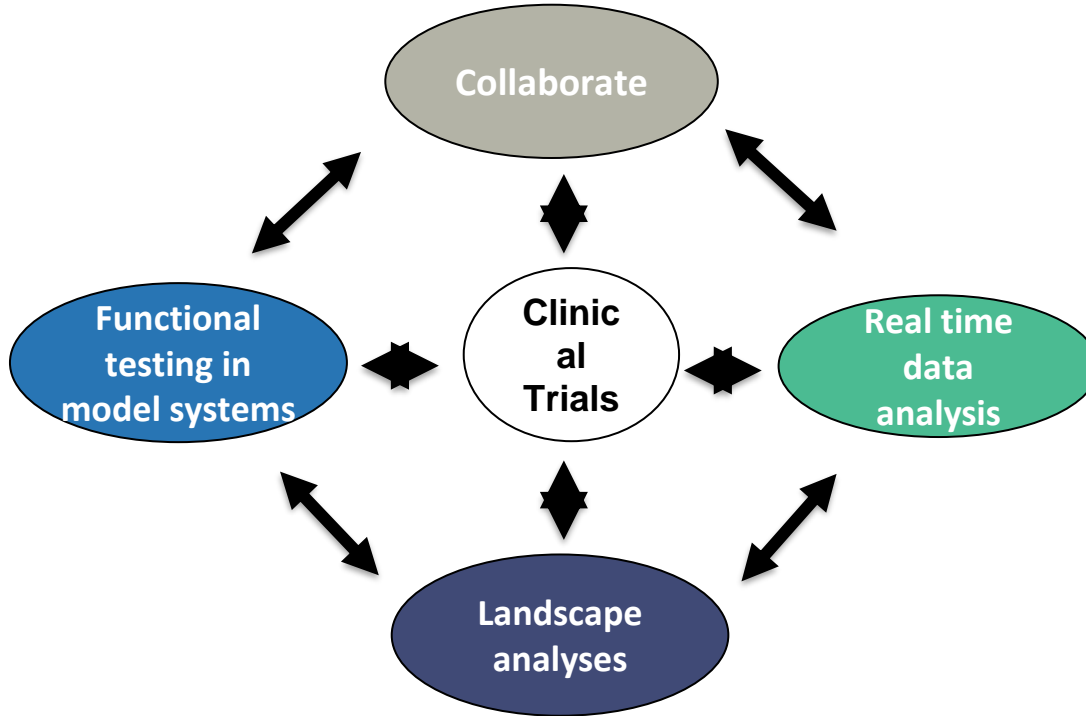
PBMC

- **Flow Cytometry**

Fecal Microbiome

Correlate with efficacy

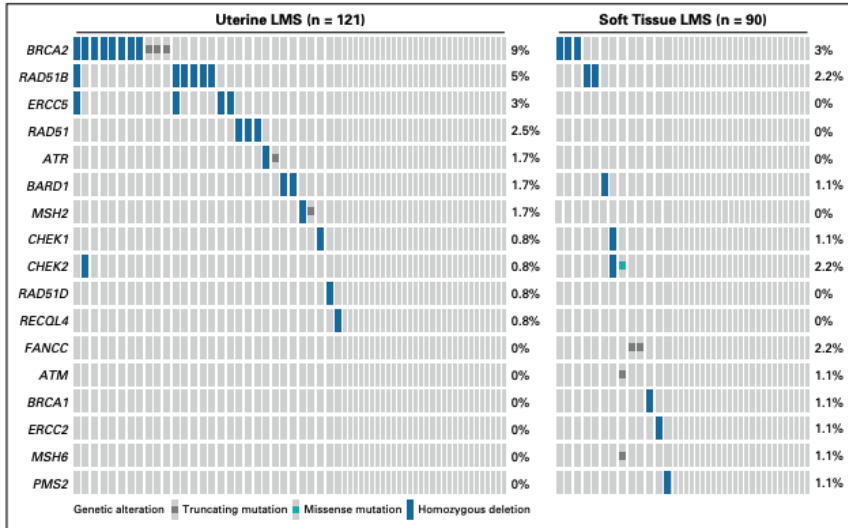
Bi-directional flow will enhance clinical trial development



Exploring PARP inhibition with checkpoint blockade in LMS leveraging DDR alterations

PRECISION MEDICINE

Clinical Outcome of Leiomyosarcomas With Somatic Alteration in Homologous Recombination Pathway Genes



Phase II Study of Rucaparib and Nivolumab in Patients with Leiomyosarcoma

Pretreatment baseline evaluation (CT scan, archival tissue)

* LMS (at least 10 uterine)
* N=20
* Unresectable/metastatic
* 1-3 prior therapies



Cycle 1

Cycle 2

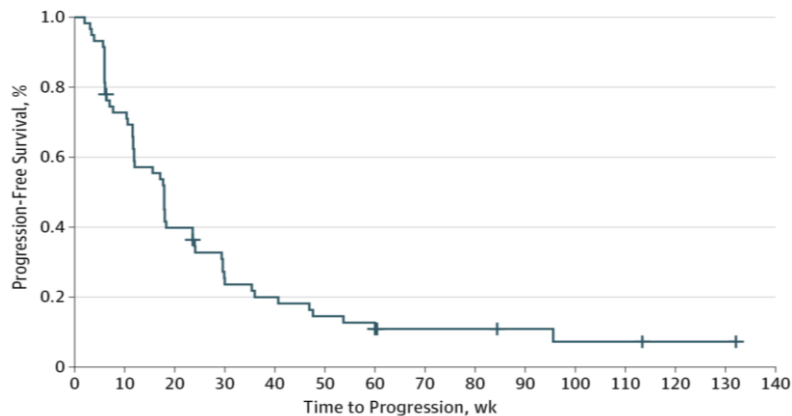
Evaluate Response Rate: RECIST 1.1 q8 weeks

Disease Progression

Rucaparib 600 mg bid days 1-28 and nivolumab 480 mg every 28 days

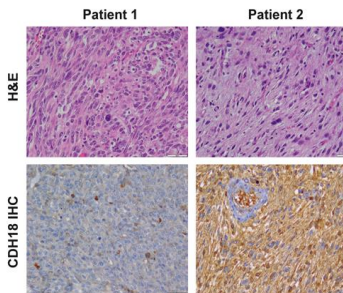
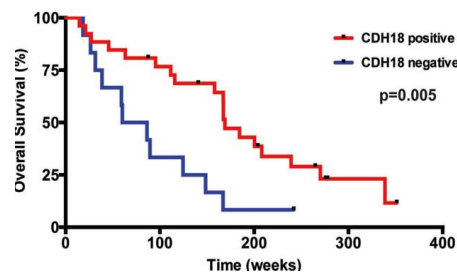
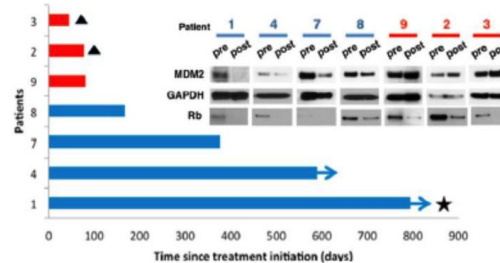
On-treatment biopsy

CDK4 inhibitors demonstrate promising progression free survival in DDLPS

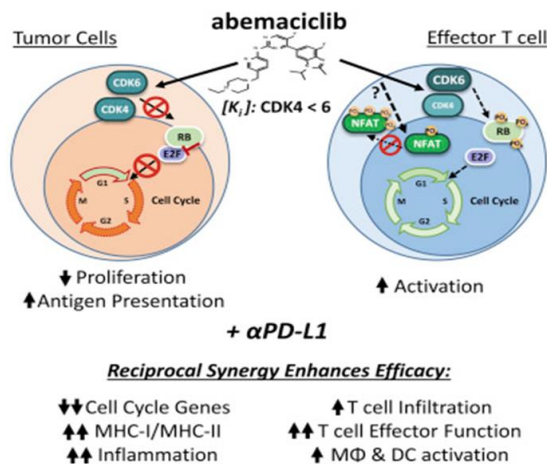


Palbociclib 125 mg PO 3 weeks on/1 off
 PFS 12 Weeks: 57 %
 Median PFS: 18 weeks

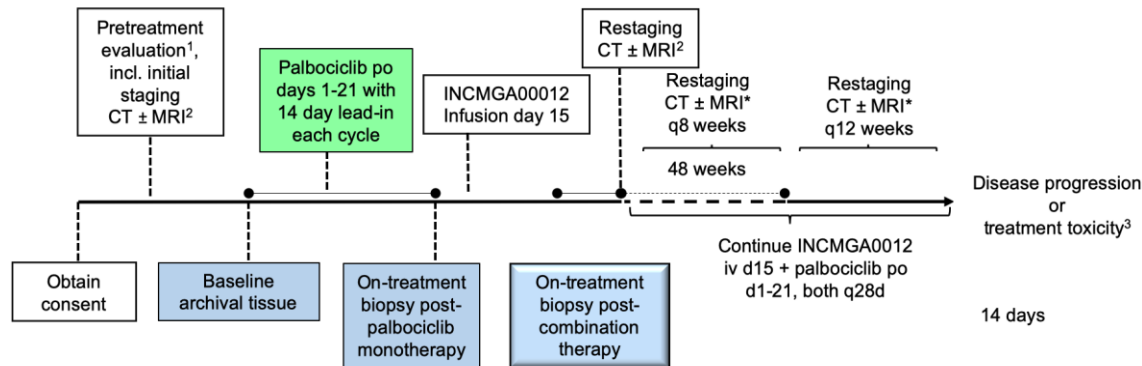
MDM2 downregulation, ATRX, and CDH18 are biomarkers senescence and correlate with efficacy



Bridging the gap between immunotherapy and cell cycle biology



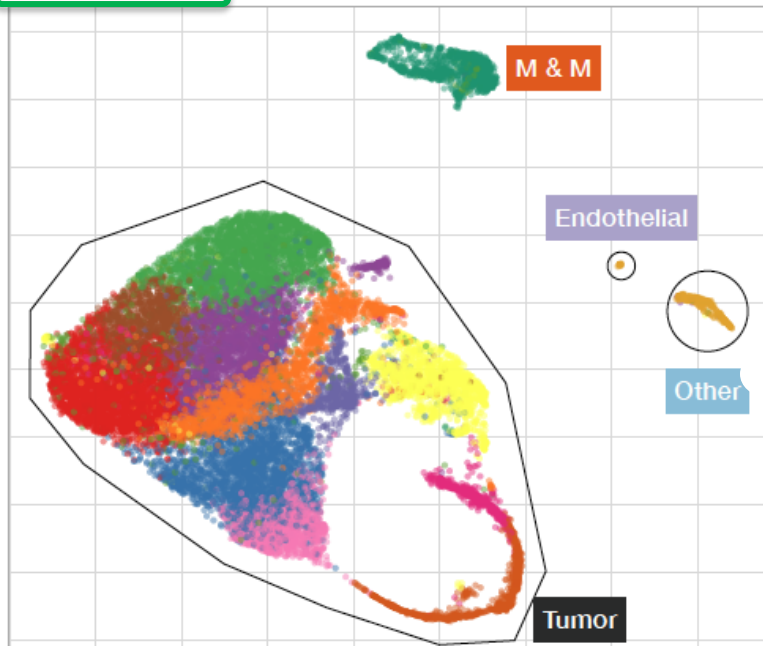
Phase II study of Palbociclib + INCMGA0012 in Dedifferentiated liposarcoma



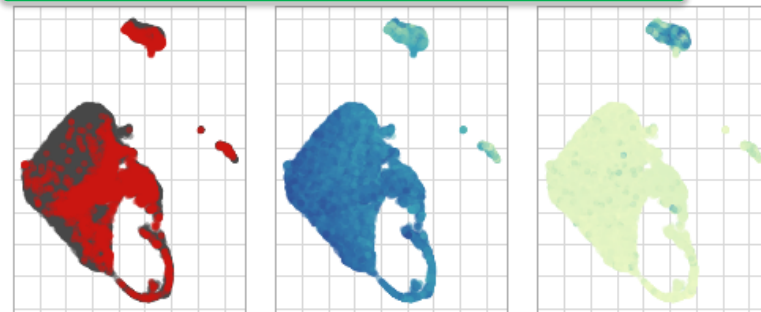
NCT04438824

Single sequencing of baseline/on-treatment DDLPS biopsy specimens

P03 (n = 19310)



Treatment Tumor Immune

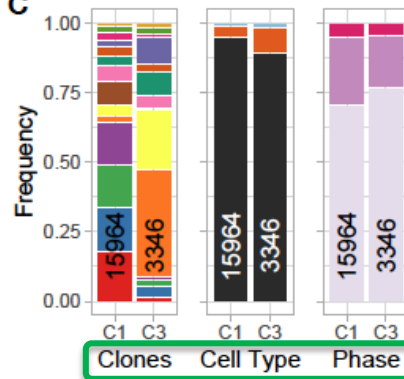


cycle
● C1
● C3
z-score
1.2
0.8
0.4
0.0

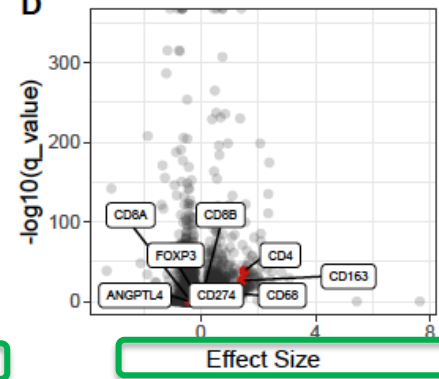
Clone
0
1
2
3
4
5
6
7
8
9
10
11
12

Phase
G1
S
G2M

C



D



Future potential targets

Cancer cell death and ag release

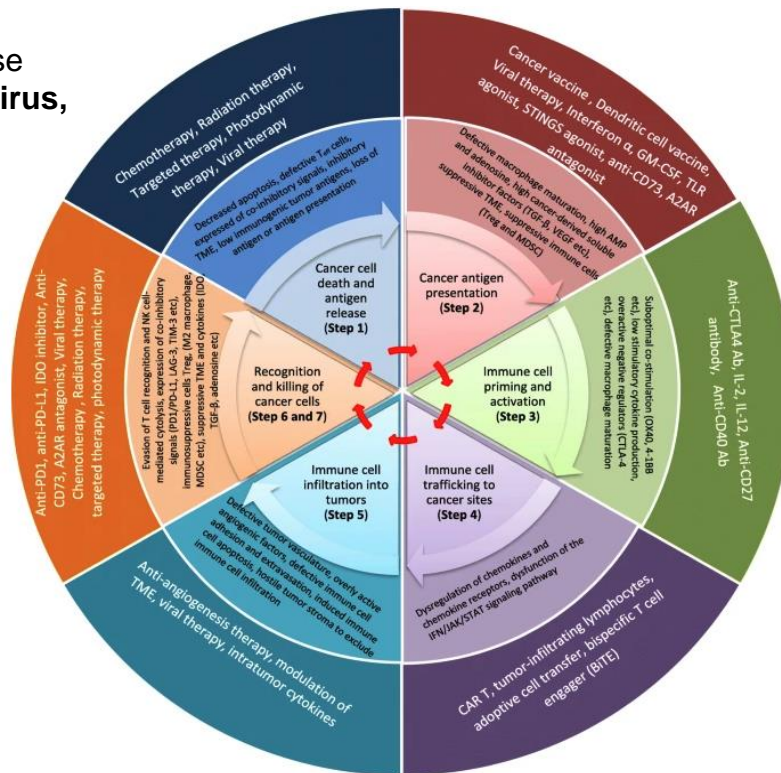
- **Viral therapy (HSV, adenovirus, measles, reovirus)**
- Targeted therapy
- Chemotherapy

Recognition killing of cancer cells/cancer antigen presentation

- **CD73**
- **A2AR antagonist**

Immune cell infiltration into tumors

- **Intratumor cytokines**
- TME modulation



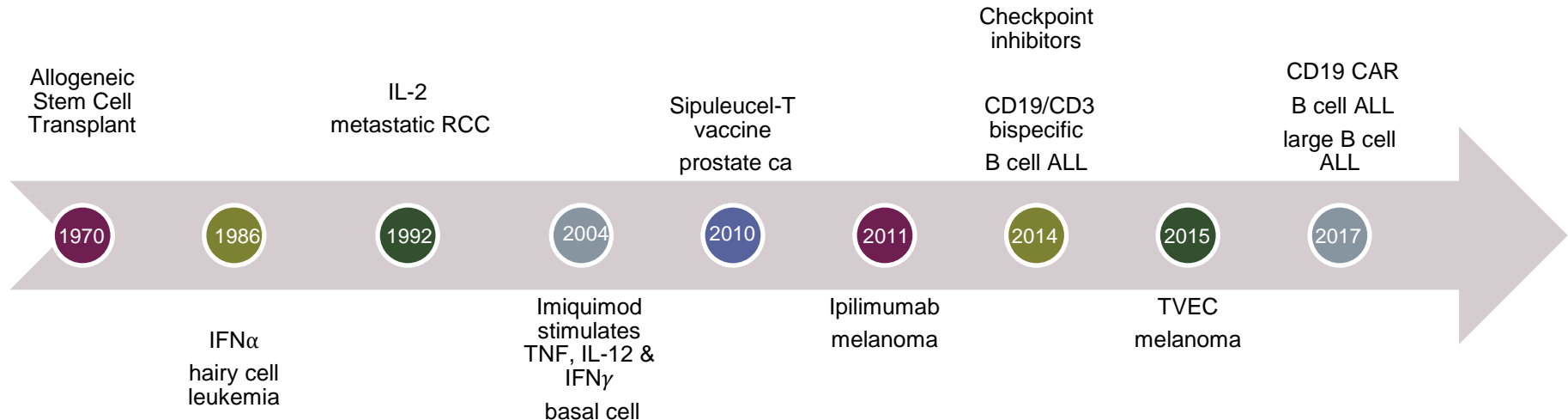
Immune cell priming and activation

- **IL-12**
- **IL-15**
- **Anti-CD40ab**
- **Anti-CD47**

Immune cell trafficking

- **Chimeric antigen receptors**

Progress of immunotherapy...Towards increased specificity



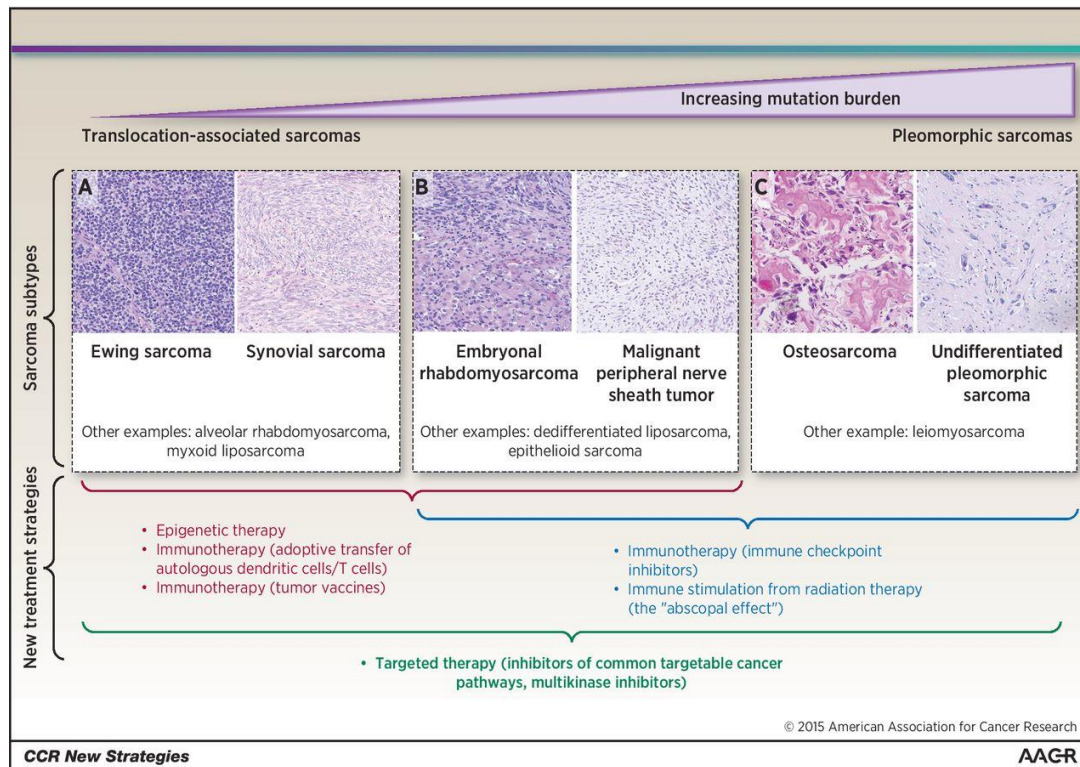
Tailoring options based on specific biology

Translocation driven sarcomas

- Adoptive cell therapy

Epithelioid sarcomas, MPNST,

- epigenetic therapy + IO



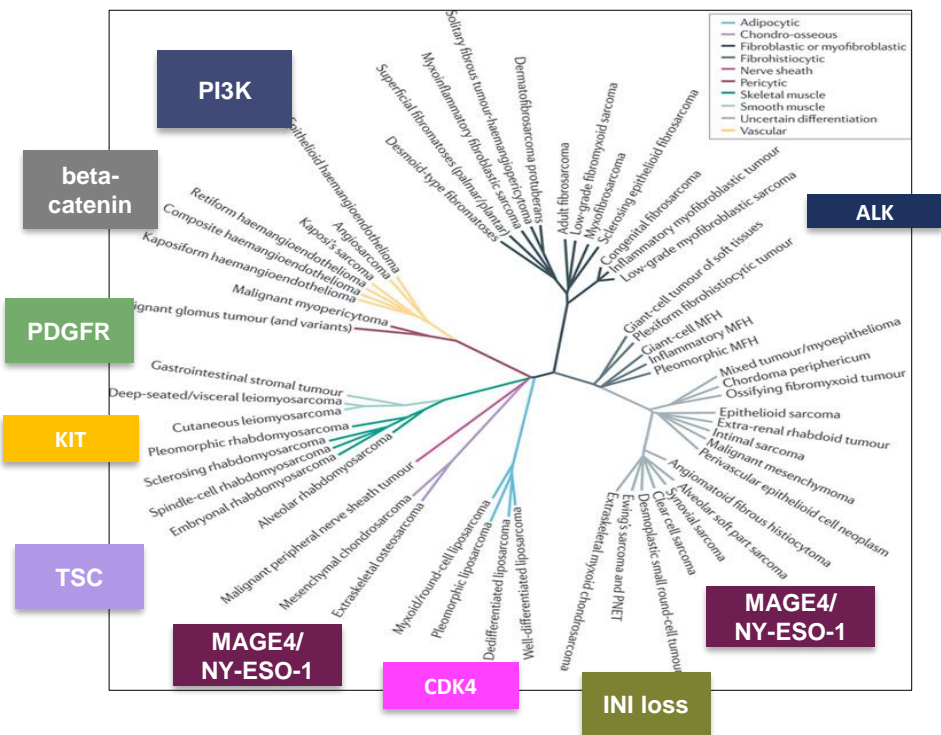
UPS (high TMB, high immune infiltrates, tertiary lymphoid structures)

- Monotherapy checkpoint blockade

LMS/Osteosarcoma

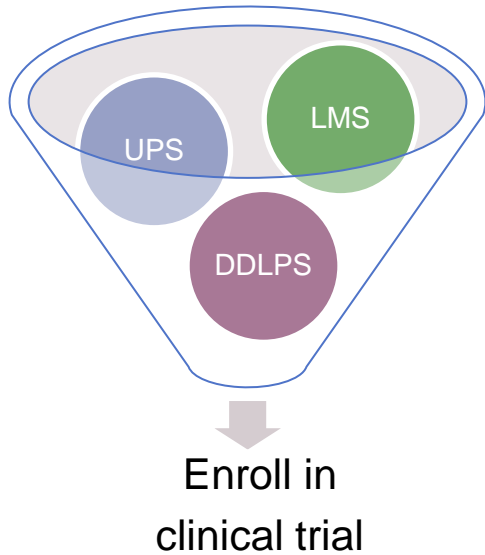
- Time to look beyond PD1 blockade
- Explore novel targets/combinations CD47, A2AR

Continue to expand IO in sarcoma, must be specific and strategic

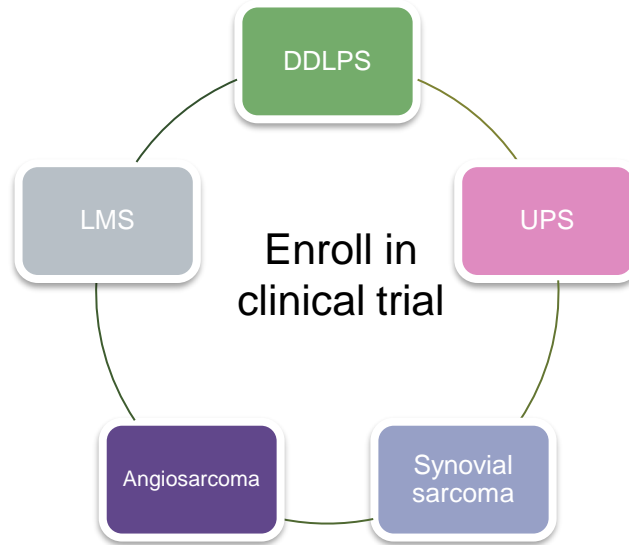


Can we take it any further?

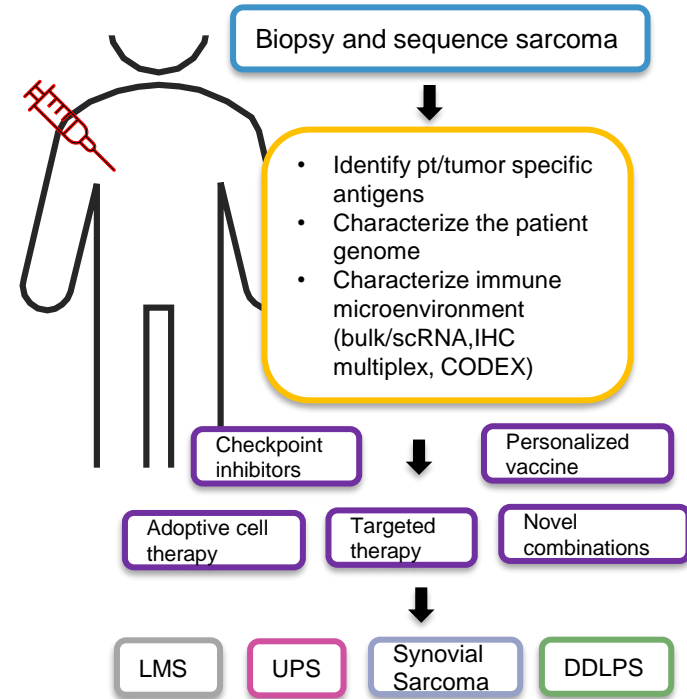
Past



Present



Future: Precision immunotherapy



Conclusions

A subset of sarcomas are immunogenic and are most likely to benefit from monotherapy checkpoint inhibition. Most others will require combinatorial strategies or alternative approaches

Biomarkers such as CD8+ T cells, tertiary lymphoid structures can identify responding tumors and while “Immune conversion” is feasible in sarcoma...it remains an uncommon event

Designing clinical trials with histology specific cohorts, pre/on-treatment biopsies while taking into account underlying biology will contribute to further characterization of the molecular and immunological features of these tumors

Bidirectional flow of information (clinical/lab) along with multi-institutional collaborations will contribute to practice changing efforts

MSK team

Sarcoma Medical Oncology

- Lauren Banks
- Jason Chan
- Ping Chi
- Mark Dickson
- Mrinal Gounder
- Mary Louise Keohan
- Ciara Kelly
- Benjamin Nacev
- Evan Rosenbaum
- William D. Tap
- Katherine Thornton
- Viswatej Avutu

Surgical Oncology

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- Sam Yoon
- Aimee Crago
- Edmund Bartlett
- Murray Brennan

Sarcoma Pathology

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- Meera Hameed
- Narsi Agaram

Pediatric Oncology

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- Emily Slotkin
- Leonard Wexler
- Paul Meyers

Early Drug Development

- Alex Drilon
- Margaret Callahan

Cellular Therapeutics

- Christopher Klebanoff
- Renier Brentjens
- Roisin O'Cearbhaill
- Chris Hackett

Support



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