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Immunotherapy and Sarcomas

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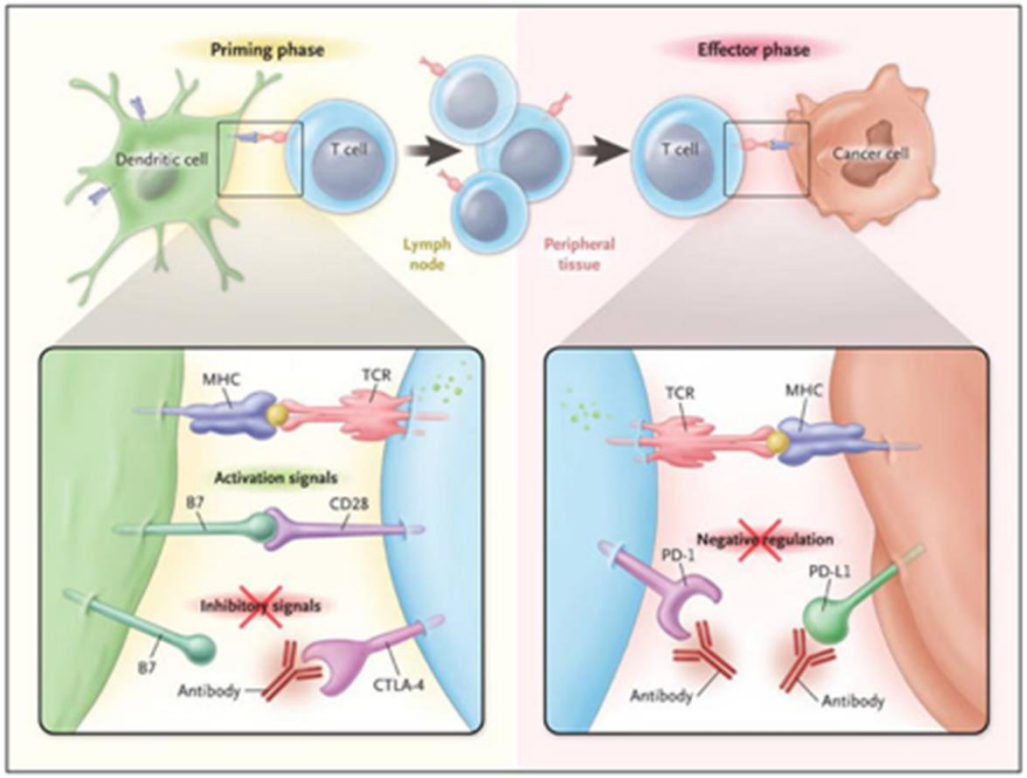
15th Annual New Orleans Summer Cancer Meeting

Soft Tissue Sarcomas and Immunotherapy

- Do checkpoint inhibitors demonstrate activity in soft tissue sarcomas?
- Is activity histology specific?
- Is single agent or combination therapy preferable?
- What are the parameters which might predict response ?
- What can we do to make tumors more immunogenic to enhance treatment response.

SARC028:
Phase II Pembrolizumab (anti-PD-1) in Soft Tissue and Bone Sarcomas



- Dose 200 mg IV q3wks
- ≤ 3 lines therapy
- STS cohorts (4):

STS	#	PR (%)
LMS	10	0
UPS	10	4 (40)
LPS	10	2 (20)
Synovial Sarcoma	10	1
Total	40	7 (18)

- PFS at 12 wks 55%, (c/w 40%)
- mPFS 18 wks

Tawbi, et al, Lancet Oncol 2017; 18: 1493–1501

Single Agent Immunotherapy
Soft Tissue Sarcoma

Agent	# Pts	ORR (%)	mPFS (m)	RR by subtype	
Ipilimumab		0	1.9	SS	Maki, 2013
Pembrolizumab (SARC028)	80	**18**	4.5	**UPS 23%** (2 CR), LPS 10%	Burgess, 2019
Atezolizumab		**42**	NR	**ASPS**	Coyne, 2018
Nivolumab		0	1.8	Uterine LMS	Ben-Ami, 2017
Nivolumab Ipilimumab + Nivolumab (Alliance 091401)	85	5 **16**	1.7 4.1	ASPS, LMS UPS 28.6, LPS 14.3	D'Angelo, 2018

ST Sarcoma histology specific response to immunotherapy

Histology	Drugs	Response Rate
UPS	Pembrolizumab Nivolumab + Ipilimumab	23% 29%
ASPS	Atezolizumab Pembrolizumab + axitinib	42% 55%
Angiosarcoma	Anti-CTLA4, Pembrolizumab, Axitinib + Pembrolizumab	71%
DDLPS	Pembrolizumab Nivolumab + ipilimumab	10% 14%
Uterine LMS	Nivolumab	0%

Tawbi et al. Lancet Oncology 2018, Chen et al. ASCO 2020, Coyne et al. CTOS 2018, Florou et al. JITC 2019, Wilky et al. Lancet Oncology 2019, Ben-Ami Cancer 2017

- **Do checkpoint inhibitors demonstrate activity in soft tissue sarcomas?**
  - YES
  - Evidence from multiple studies identifies response ≈ 20%
  - Acceptable activity of Pembrolizumab monotherapy
  - Nivolumab monotherapy did not meet established response criteria for further study

- **Is activity histology specific?**
  - YES
  - Significant responses in alveolar soft part sarcoma (ASPS)/atezolizumab; angiosarcoma
  - Responses in “common” histologies are primarily observed for UPS > LPS
  - Minimal activity in tumors with single or isolated genetic alteration
    - e.g., synovial sarcoma, Ewing's, GIST

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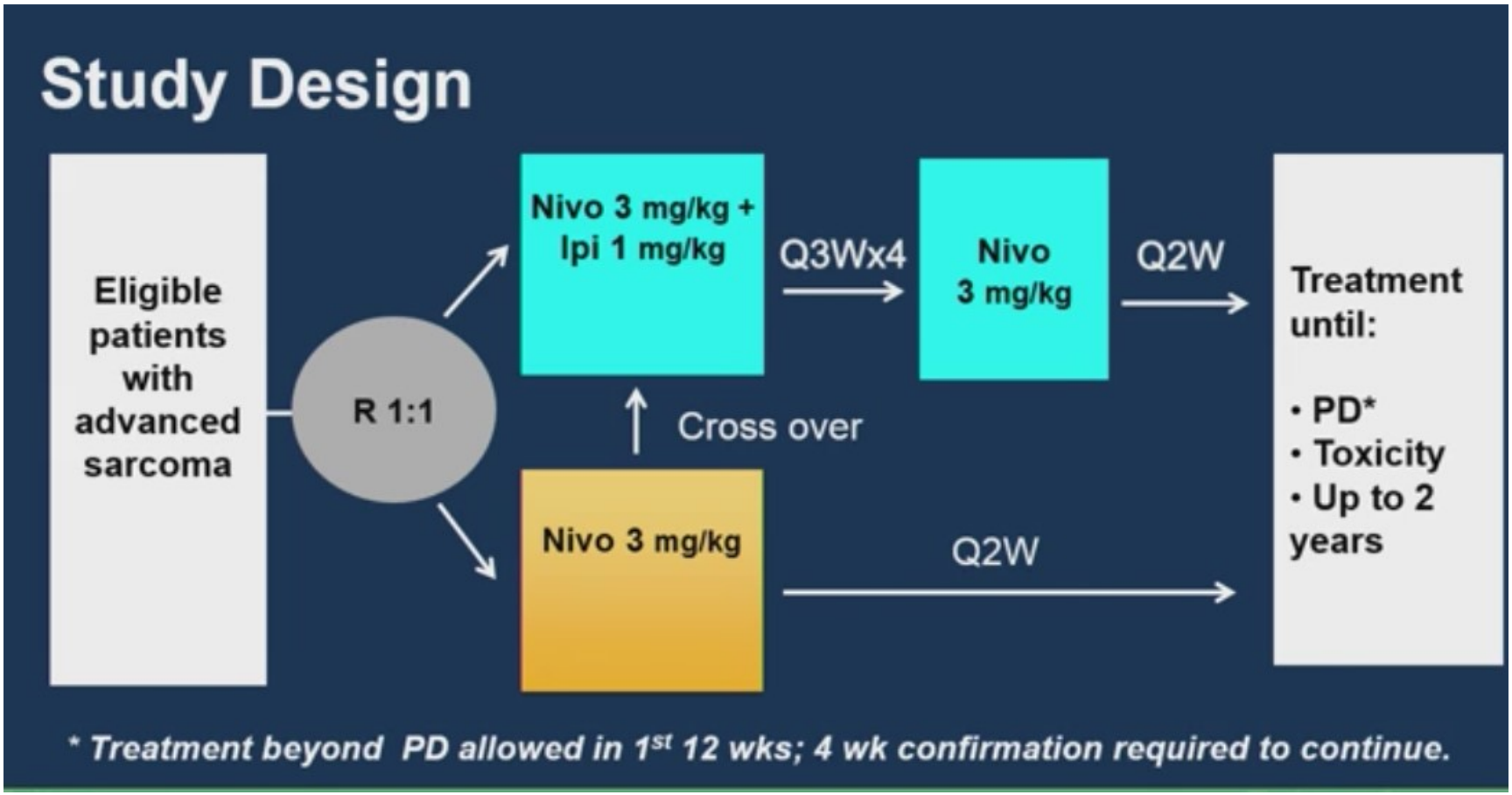
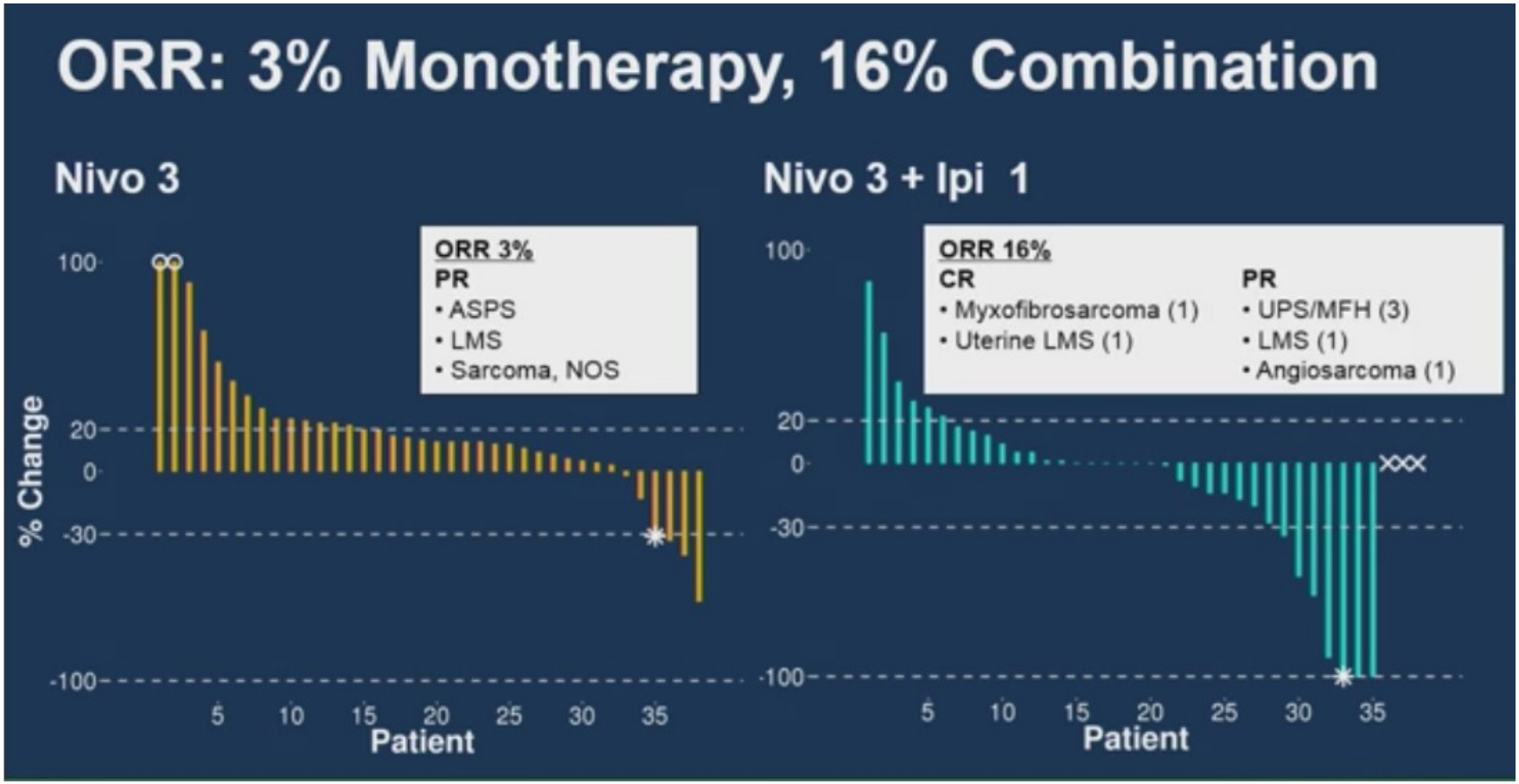
Alliance 091401 Trial



D'Angelo, ASCO 2017

ORR: 3% Monotherapy, 16% Combination



A091401 Expansion cohort

	GIST (n=18)		DDLS (n=24		UPS (n=24)	
Treatment	N	N+I	N	N+I	N	N+I
Evaluable Design	9	9	12	12	12	12
Median age (range)	69 (41-79)	62 (40-81)	62 (27-82)	59 (46-68)	64 (34-85)	60 (44-84)
% female	20	46	53	36	36	53
% ≥3 regimens	80	46	33	43	50	40
%≥ Grade 3 TRAE	10	46	20	14	15	14
6mth RR n%, (CI)	0, 0% (0-31%)	0, 0% (0-28%)	1, 7% (0.2-32%)	2, 14% (2-43%)	1, 8% (0.2-36)	2, 14% (2-43%)
Response Duration[b]	-	-	4.5	8.3 & 13.1	14.6	7 & 7.6
Median PFS[b]	1.5 (1.3-10)	2.9 (1.4-NE[c])	4.6 (3.2- NE)	5.5 (2.8 - NE)	1.5 (1.4-NE)	2.7 (1.5 - NE)
Median OS[b]	9.1 (4.9-NE[c])	12.2 (6-NE)	8.1 (7-NE)	13.1 (9.1-NE)	6.6 (2.4-17.6)	NE (5.1-NE)

Chen et al ASCO 2020

Agent	ORR (%)	mPFS (m)	RR by subtype	
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Nivolumab Nivolumab +Ipilimumab	5 **16**	1.7 4.1	ASPS, LMS UPS 28.6, LPS 14.3	D'Angelo, 2018
Durvalumab/Tremelimumab	**14.3**	2.8	**ASPS 50%,** chordoma 20%, AS/UPS 20%	Somaiah, 2020

- **Is monotherapy or combination immunotherapy preferable?**
  - ???
  - Pembrolizumab monotherapy has substantial activity in specific sarcoma subtypes
  - Combination IO/IO achieves higher response rate compared to Nivolumab monotherapy (16% v 5%), comparable to Pembrolizumab monotherapy
  - Responses to combination immunotherapy in heavily pretreated population (16%, mPFS 4.1) are comparable to first line single agent (doxorubicin) chemotherapy (15-18%, mPFS 4-6 m)
  - Toxicity of combination is more substantial than monotherapy, but tolerable
    - Gr 3/4 AE: N+I 48% v N 40%
    - Anemia (17%), hypotension (10%), hyponatremia (7%)

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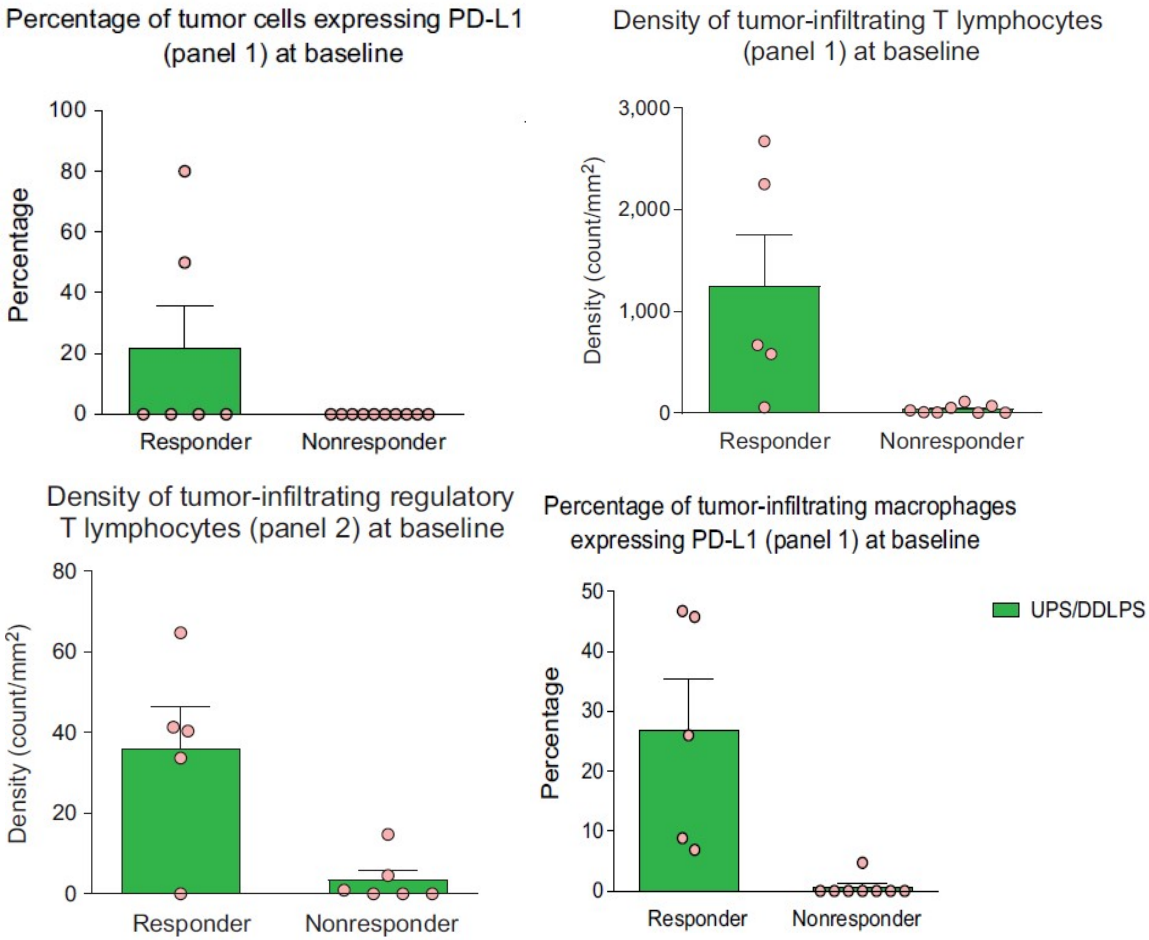
Assessment of baseline immune status in SARC028

- Baseline biopsy characteristics associated with response:
  - Increased tumor cell expression of PD-L1
  - Increased tumor IL
  - Increased PDL-1 macrophages
  - Increased antigen experienced T cells
  - Increased T regulatory cell infiltration

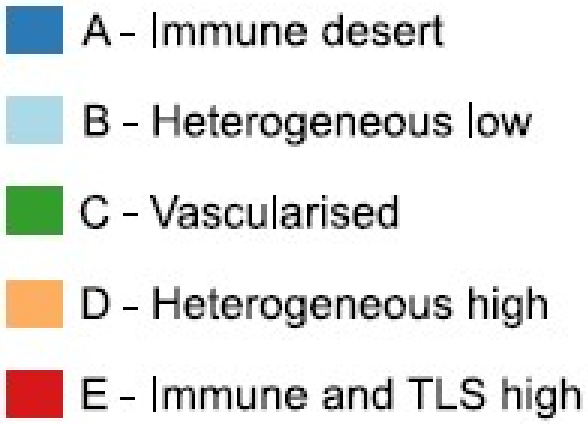


Keung, et al Clin Cancer Res 2020; 26(6):1258-66

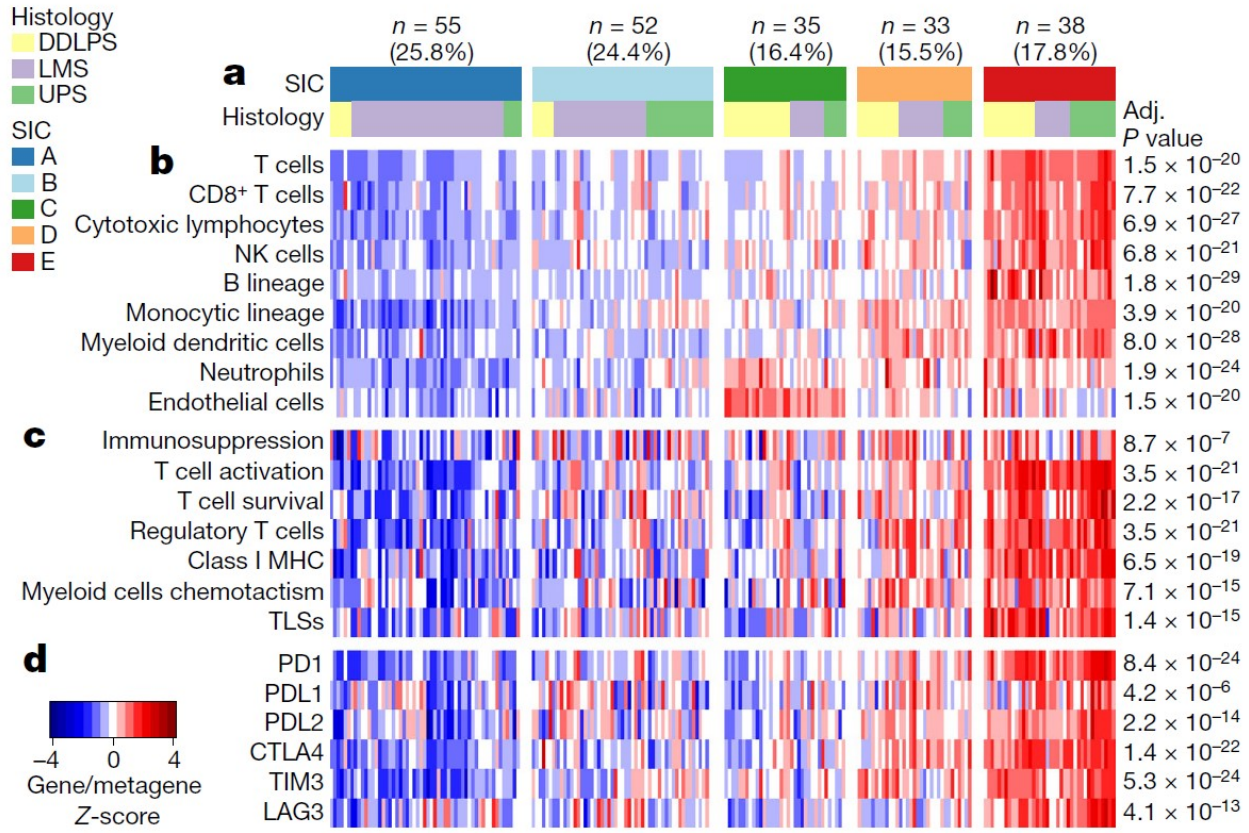
Sarcoma Immune Classification (SIC)

Petitprez, Nature, January 2020

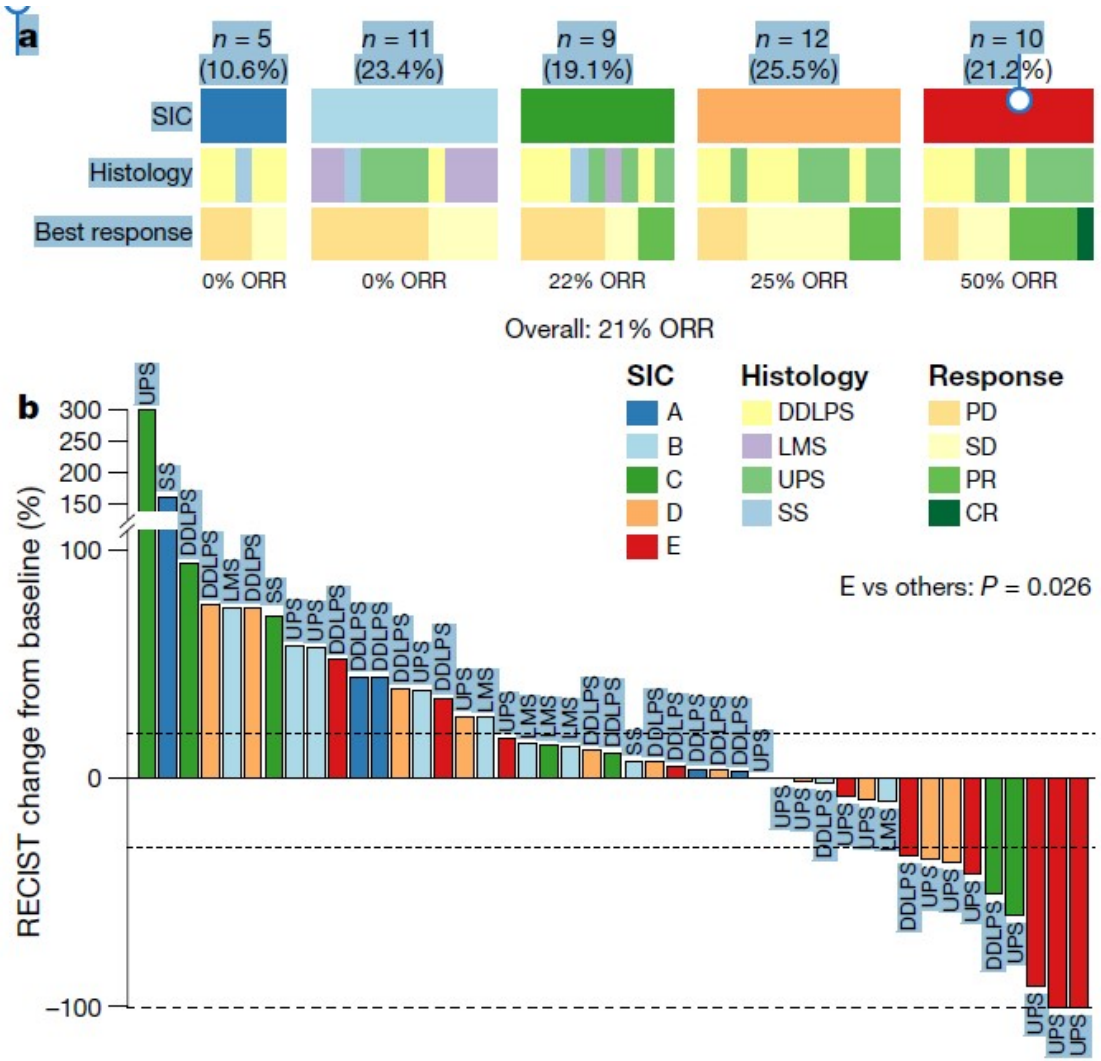
- Gene expression profiling of 4 independent cohorts
  - Composition of tumor microenvironment (TME) by MCP counter
    - e.g., T cells, NK cells, dendritic cells, endothelial cells, B cells
  - Functional orientation of immune TME incl tertiary lymphoid structures (TLS)
  - Expression of genes related to immune checkpoints
  - Association of SIC profile with histology



Sarcoma Immune Classification (SIC)/Sarc028



Petitprez, et all Nature, 2020, 577:556



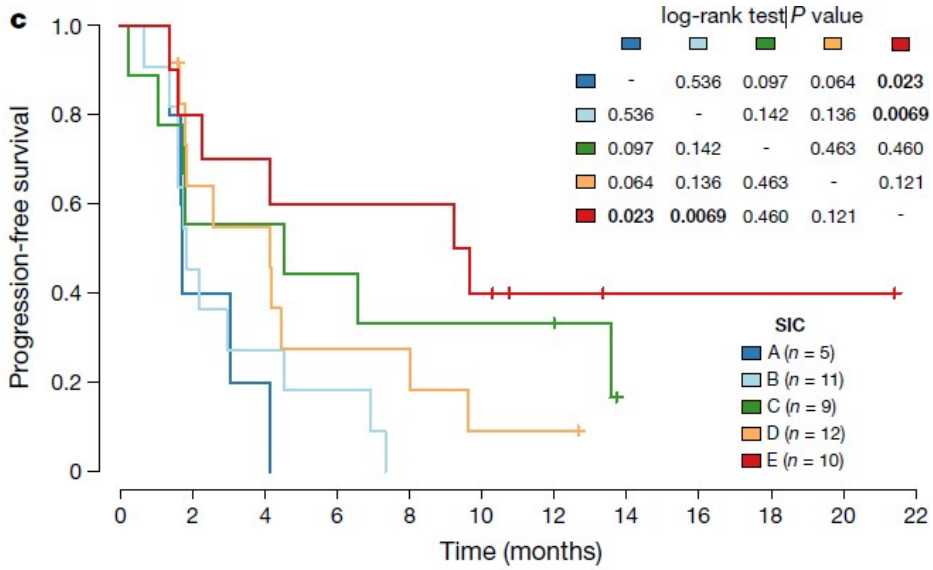


Fig. 4 | SICs are strongly associated with STS response to PD1 blockade

irAE and response

- Immune related toxicity associated with clinical benefit (Rosenbaum)
  - 124 pts

Immune related AE	+	-
Durable clinical benefit	53%	29%
Median PFS (mos)	16.6	10.6
RR	Gr 3/4 33% Gr 1/2 15% None 6%	

- Dual therapy > RR than monotherapy, but increased toxicity
  - I/N v N (Alliance A091401)

Biomarkers and ST Sarcoma

- Responses associated with
  - Baseline tumor immune status (SARC028)
  - Sarcoma Immune Classification (SIC): “Hot”
    - Heterogeneous High
    - Immune and TLS high
  - Immune related adverse effects (irAE)

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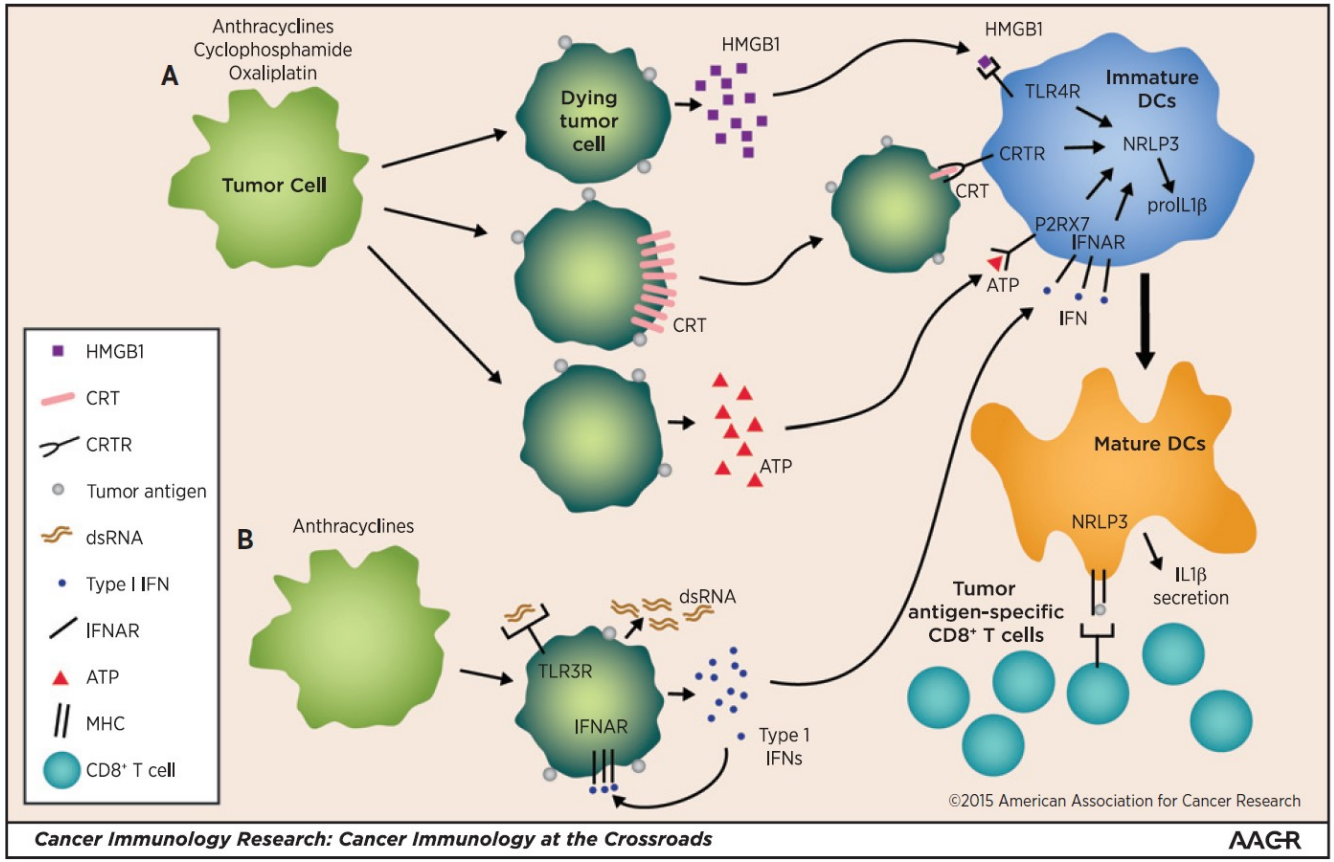
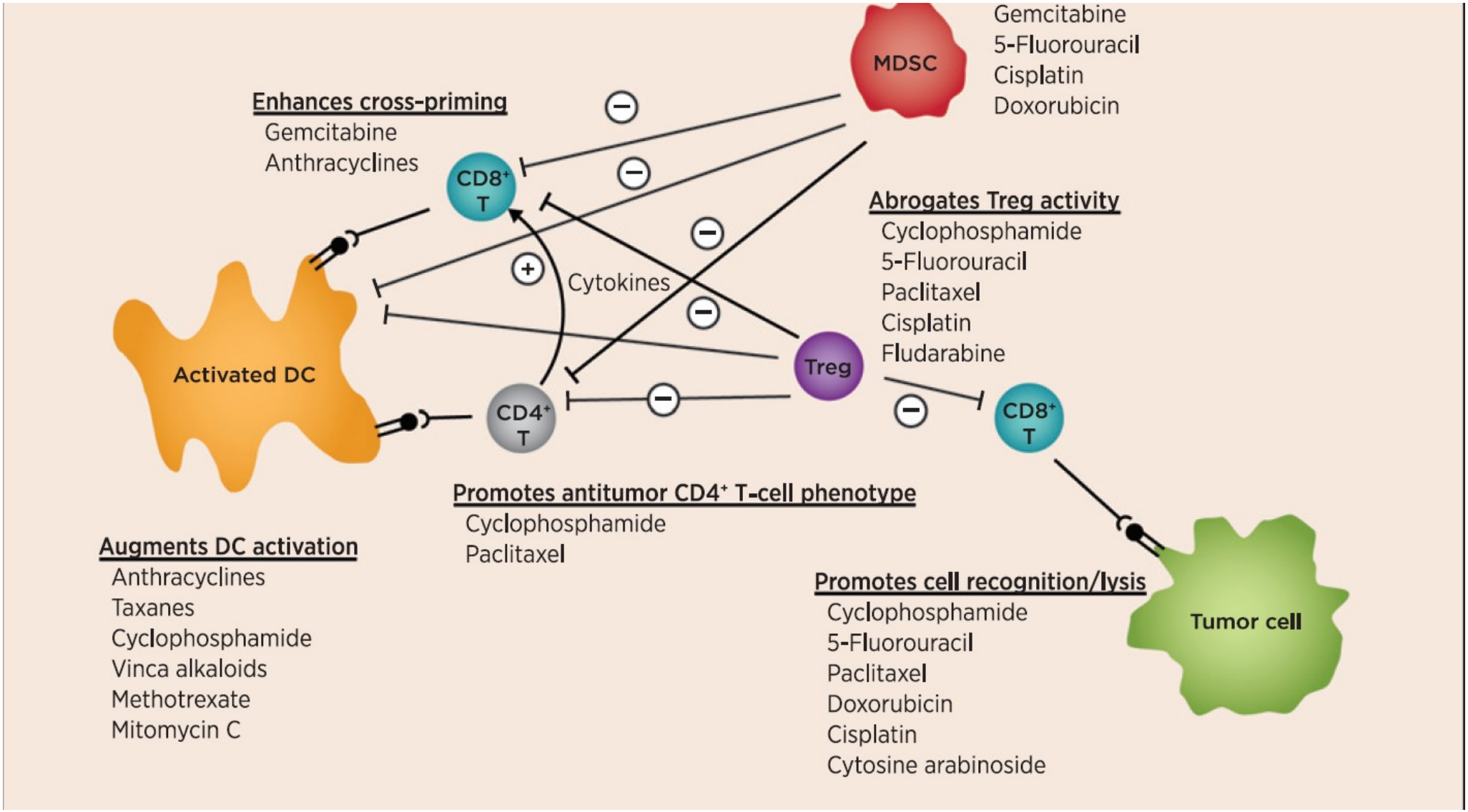


Dying Tumor cells release:

- "danger" associated molecules:
  - HMGB1
  - ATP
- CRT (calreticulin) –> phagocytosis signal
- type I IFN

Results in dendritic cell maturation and evolution of tumor specific CD8+ T cells


MDSC
Gemcitabine
5-Fluorouracil
Cisplatin
Doxorubicin
Enhances cross-priming
Gemcitabine
Anthracyclines
CD8+ T
Abrogates Treg activity
Cyclophosphamide
5-Fluorouracil
Paclitaxel
Cisplatin
Fludarabine
Cytokines
Activated DC
Treg
CD4+ T
CD8+ T
Promotes antitumor CD4+ T-cell phenotype
Cyclophosphamide
Paclitaxel
Augments DC activation
Anthracyclines
Taxanes
Cyclophosphamide
Vinca alkaloids
Methotrexate
Mitomycin C
Promotes cell recognition/lysis
Cyclophosphamide
5-Fluorouracil
Paclitaxel
Doxorubicin
Cisplatin
Cytosine arabinoside
Tumor cell

IO/chemo combinations

Agent	ORR (%)	mPFS (m)	RR by subtype	
Pembrolizumab	18	4.5	UPS 23% (2 CR), LPS 10%	Burgess, 2019
Pembrolizumab + Doxorubicin	22	7.8	UPS 66%, LPS 40%, LMS 30%	Pollack, 2019
Pembrolizumab + Cyclophosphamide	2	1.4	SFT	Toulmonde, 2018
Pembrolizumab + Eribulin	5.3	2.8	LMS	Nathenson, 2020
Pembrolizumab + Axitinib	25	4.7	ASPS 54.5; non-ASPS 9.5	Wilky, 2019
Nivolumab	5	1.7	ASPS, LMS	D'Angelo, 2018
Nivolumab + Sunitinib	9.3	5.9	AS, ESMC, SS, ASPS	Martin-Broto, 2019
Nivolumab + Ipilimumab + Trabectedin	22	NR	Multiple	Chawla, 2019

ASCO 2020

- Doxorubicin + Pembrolizumab (Livingston, et al)
  - 30 pts
  - multiple histologies
  - RR 36% (LPS 2/7, LMS 4/10, 3/3 UPS), 1 CR
  - mPFS 6.9 m, OS 12 m
  - Gr 3/4 AE 33%
  - Compares favorably with single agent Doxorubicin activity: 16%
- Ipi + Nivo + Trabectedin, SAINT regimen (Gordon, et al)
  - 41 pts, first line
  - RR 19.5% (3 CR); 2/8 LMS, 1/8 LPS, 3/6 UPS, 1/3 SS, 1/1 clear cell sarcoma
  - 6m PFS 56%, OS >12.5m
  - Gr 3 AE 54%
- Ipi + Nivo (Zer, et al)
  - 15 pts, prior treated
  - Classic Kaposi's sarcoma
  - ORR 71%, independent of TMB and PDL-1 status

Conclusions

- Immunotherapy demonstrates consistent low-level activity in heterogeneous populations of soft tissue sarcoma patients
- Response appears histology specific
  - UPS, ddLPS
  - ASPS
- IO/IO results in higher response rates associated with increased toxicity
- At present efforts to increase immunogenicity have had limited effect
  - IO/doxorubicin compares favorably with single agent doxorubicin
- Predictors of response include
  - Baseline tumor immune status: tILs, PDL-1 expression
  - Sarcoma Immune Classification (SIC) gene profile
  - Immune-related adverse events (irAE)

Thank You !!