Immunotherapy in Sarcoma: Where Do We Go From Here?

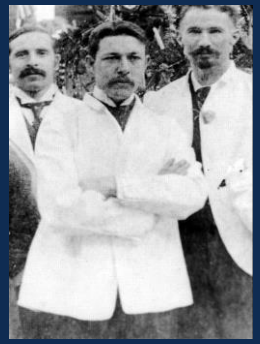
Breelyn A. Wilky, MD

Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine

PRESENTED AT: ASCO ANNUAL MEETING '16

Timeline of Immunotherapy in Sarcoma

1890s



William Coley

1980 - 2005

Cytokines +/- chemo

- IL-2 (high dose)
- IFN-α/β
- mifamurtide

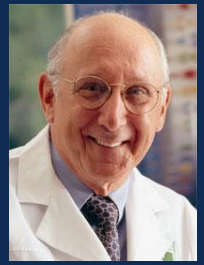
2005 - 2012

Vaccines

- Autologous tumor cells
- Dendritic cells
- GVAX

2010

Adoptive T cell therapy – NY-ESO-1^{+} synovial sarcoma



2013 - today

Checkpoint inhibitors

Wilky and Goldberg, Discov Med 2014

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The Yin and Yang of the Immune Response

Pro-inflammatory

- Infiltrating cells
  - $CD8^+$ effectors
  - $CD4^+$ T1/T2
  - Mature DC
  - TAM M1
  - NK/NK T cells
- Complement activation & ADCC
- Cytokines
  - IFN-γ, IFN-α/β, IL-12, TNF, NKG2D, TRAIL, perforin

Anti-inflammatory

- Infiltrating cells
  - $CD8^+$ anergic/exhausted
  - $CD4^+$ T reg
  - MDSC (TAM M2)
  - immature DC
- Cytokines
  - VEGF, IL-10, GCSF, TGF-β, IDO/KYN
- Checkpoint proteins

Loveland, Nat Immunol 2008

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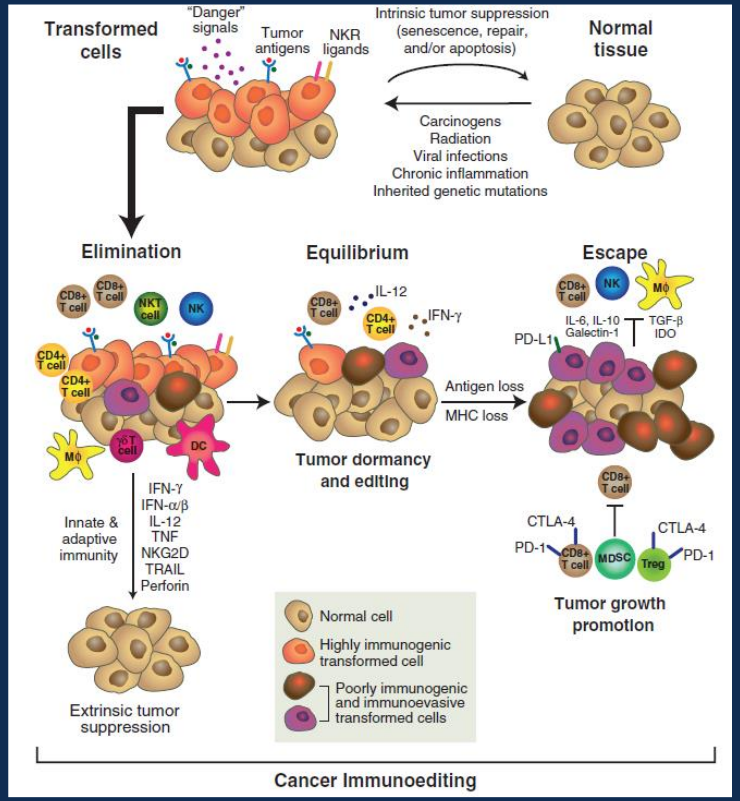
The Cancer Immunoediting Hypothesis



- Immunosurveillance
- Immunoediting
- Escape

Schreiber, Old, Smyth Science 2011

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Mechanisms of Immune Evasion by Cancer

Intrinsic tumor cell changes

- Loss/lack of neoantigens & MHC
- Expression of suppressive cytokines or checkpoint proteins

Tumor microenvironment

- Anti-trafficking cytokines
- Impaired angiogenesis and poor tumor blood flow

Alterations to tumor-infiltrating immune cells

- Shift in ratio of suppressive/activated immune cells (Treg, MDSC, TAM)
- Expression of checkpoint proteins on $CD8^+$ T cells
- Soluble suppressive factors leading to exhausted state (IDO/KYN pathway)

Callahan, Primer Session at SITC Annual Meeting 2015, Washington DC

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Strategies for Immunotherapy

	Target	Therapeutic Strategy
	Immunogenic tumor-specific antigens	Vaccines
	Effective antigen presentation/recognition	DCs, oncolytic viruses, agonists
	Antigen-specific T cell production	Adoptive T Cell therapy
	Improve T cell localization within tumor	Microenvironment
	T cell ratio effector > anergic	Immunostimulatory receptors
	Counteract immunosuppression	Checkpoint blockade, anti-Treg

Adapted from Jedd Wolchok and others

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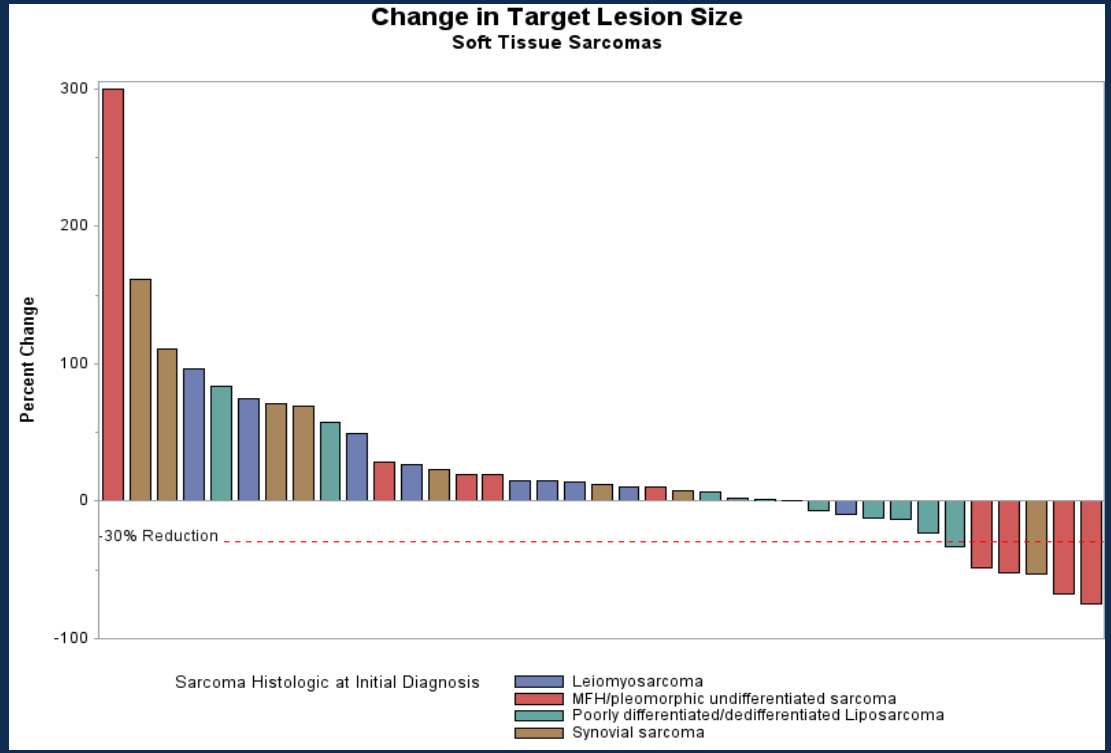
Abstract 1 – SARC 028 Pembrolizumab

- 11/37 with tumor regressions, UPS, dedifferentiated LPS, and synovial sarcoma
- Overall 19% ORR rate by RECIST, additional 40% of patients with best response of stable disease
  - Melanoma 33%
  - NSCLC 19%
  - >20% ORR gastric, bladder, head and neck



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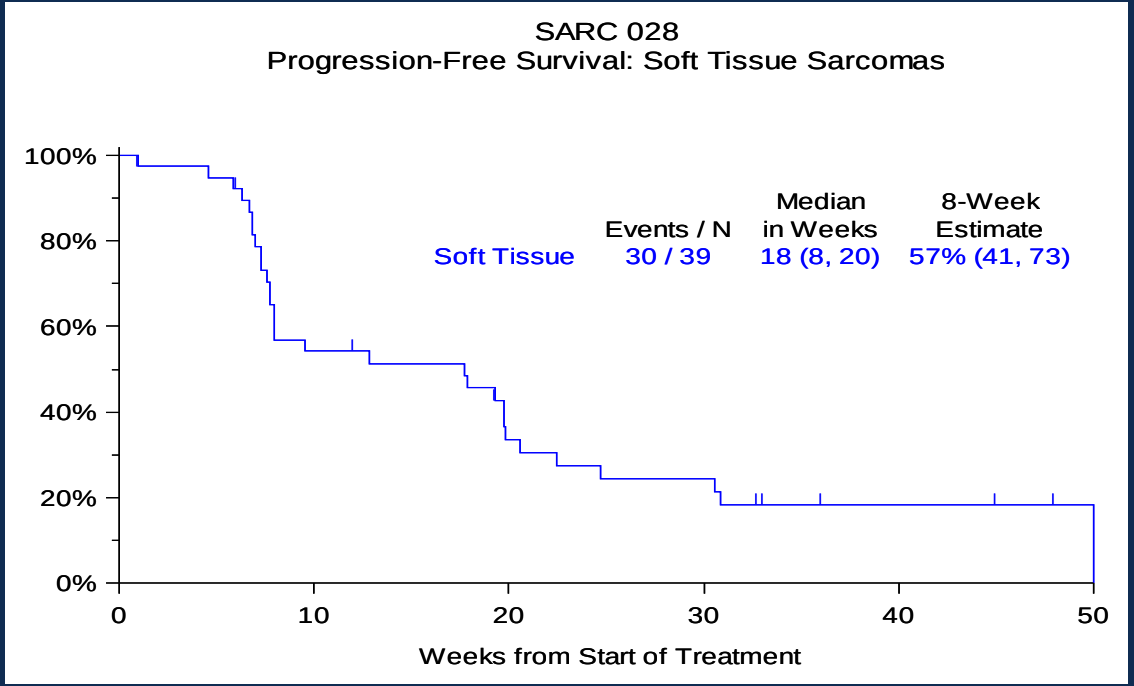
Abstract 1 – SARC 028 Pembrolizumab

- Median F/U- 7.5 months
- **4-months PFR 44% [C.I., 22%-66%] statistically significant improvement relative to historical control PFR rate (20%)**



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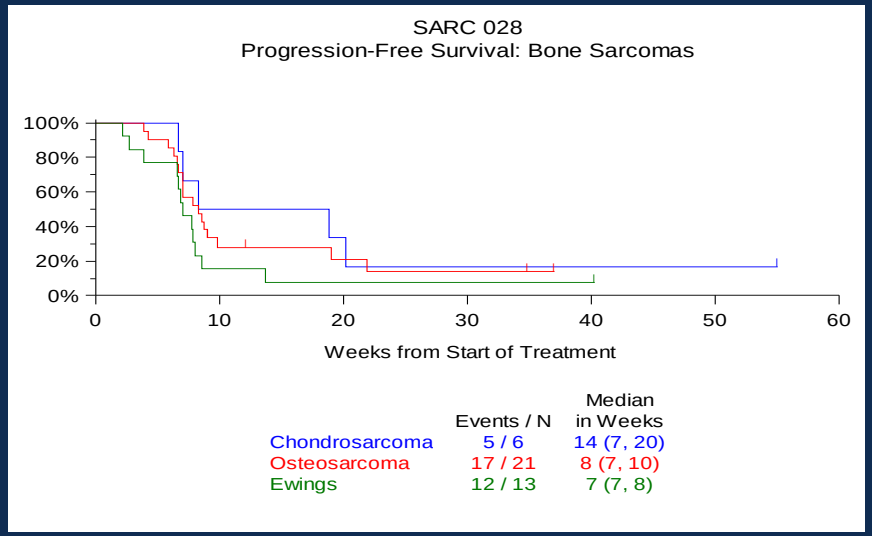
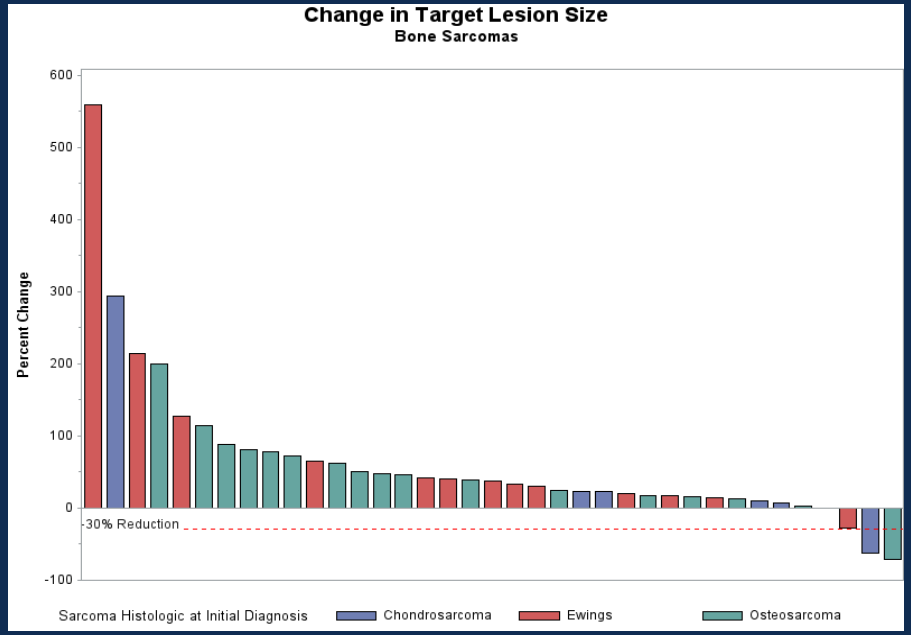
Abstract 1 – SARC 028 Pembrolizumab

- 3 patients with partial responses





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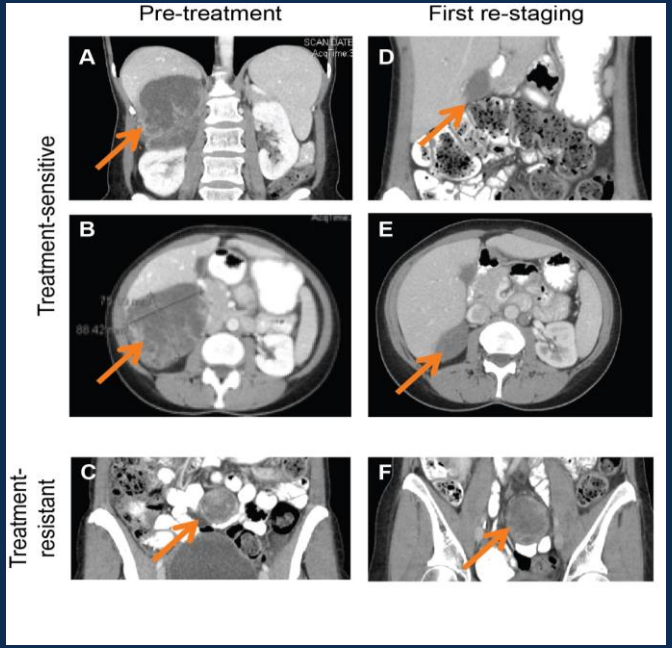
Abstract 2 – Phase 2 Nivolumab for uLMS

- 12 patients – small numbers
- All with progressive disease at 3 month scans
- Consistent with lack of response for LMS in SARC 028
- However one exceptional responder reported separately



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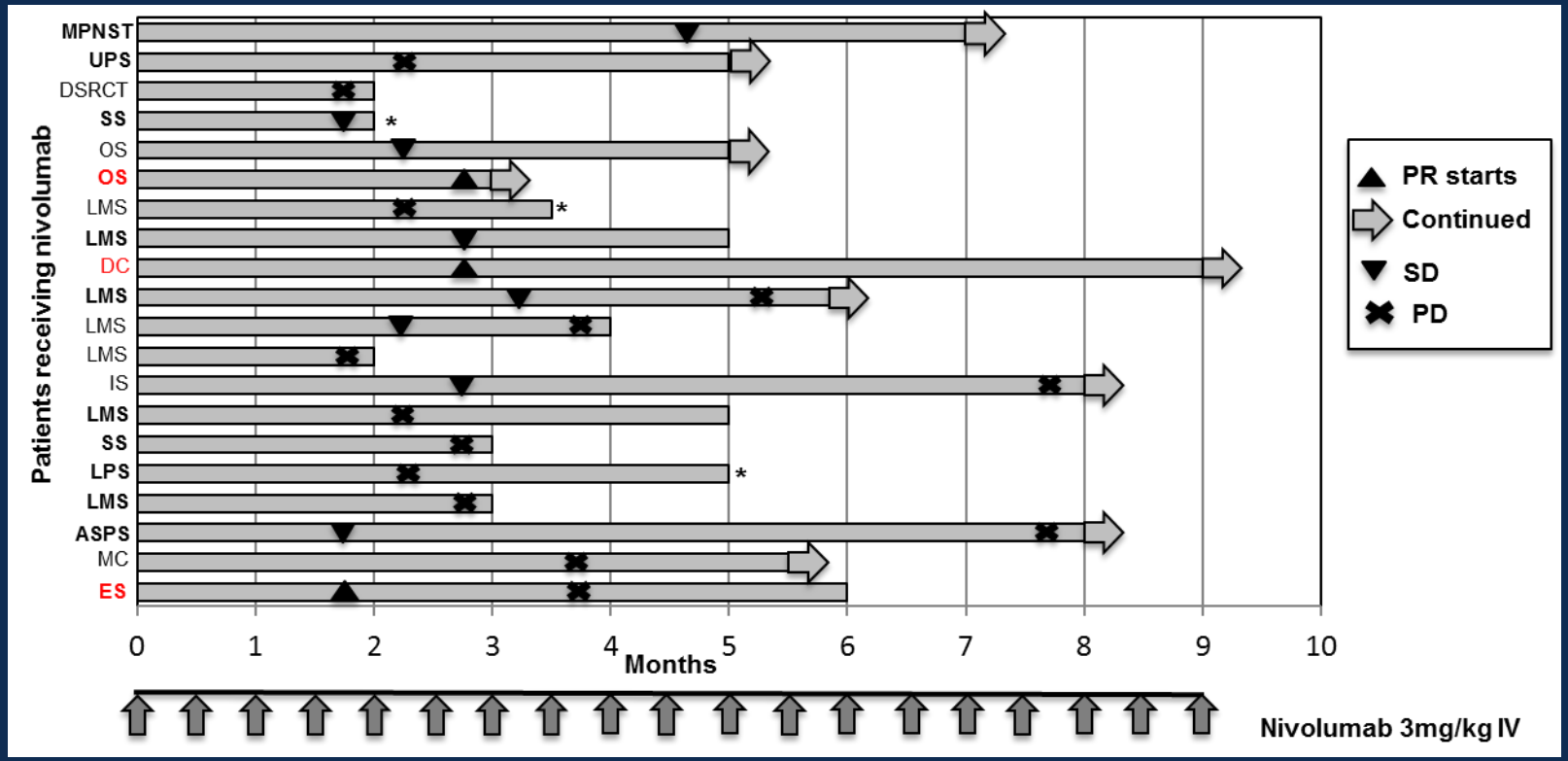
Response in 20 patients who received at least 4 doses of Nivolumab (Paoluzzi L, Rosen G et al., abstract 11047)



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PD-1 Inhibitor Monotherapy for Sarcoma

- No unexpected toxicities
- Response rate and PFR meet pre-defined activity benchmarks for soft tissue sarcoma arm
- RECIST best way to assess response, particularly bone sarcomas?
- Immunotherapy may impart overall survival benefit even after initial progression or improve response to subsequent therapies – longer follow up required
- Moving forward with expansion trials in histology-based cohorts may miss rare responders in other subtypes (ie LMS, synovial, dediff chondro)
- Critical need for biomarkers of response to checkpoint inhibitor therapy

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Potential Predictive Biomarkers for Checkpoint Blockade

- Tumor PD-L1 expression? Most tumors, but some responders even in PD-L1 negative tumors (RCC, melanoma, squamous NSCLC)
- PD-1/PD-L1 expression on TIL (Bladder, melanoma)
- Presence of $CD8^+$ TIL, particularly at tumor invasive margin (melanoma)
- High somatic mutation burden (MMR deficient colorectal cancer, melanoma, NSCLC)
- Low Tregs/MDSC in tumor OR peripheral blood (melanoma)
- Elevated IDO1/2 and KYN (linked to anti-CTLA4 activity in melanoma)
- And many more…

Meng et al, Cancer Treat Rev 2015; Hamid et al J Transl Med 2011

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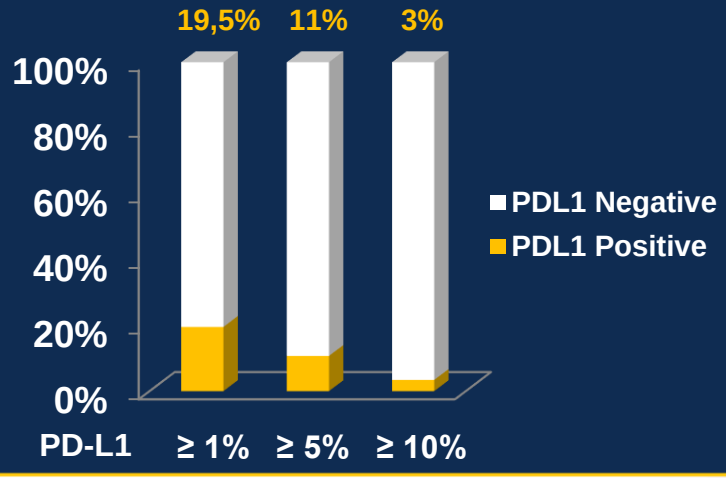
PD-L1 Expression in Sarcoma

- About 20% positivity in sarcomas
- Problems with PD-L1 as biomarker (staining, transient expression, heterogeneity)
- May not be required for response
- Await analysis of responders in Tawbi trial



	IHC PDL1 % positive		IHC PD1 % positive		IHC PDL2 % positive	
	malignant cells	non-malignant cells	malignant cells	non-malignant cells	malignant cells	non-malignant cells
7	0	NA	0	NA	90	na
9	0	20	0	0	80	0
2	1	2	0	0	20	5
6	0	10	0	0	40	0
1	0	5	0	0	90	0
10	0	na	0	0	80	na
8	0	20	0	0	10	0
11	0	20	0	5	30	0
3	10	1	0	0	20	0
5	20	0	0	5	90	0

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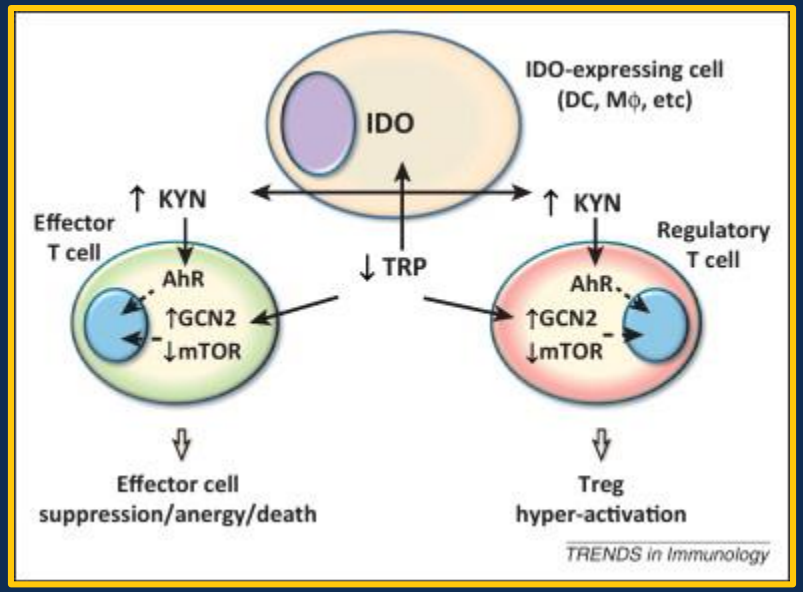
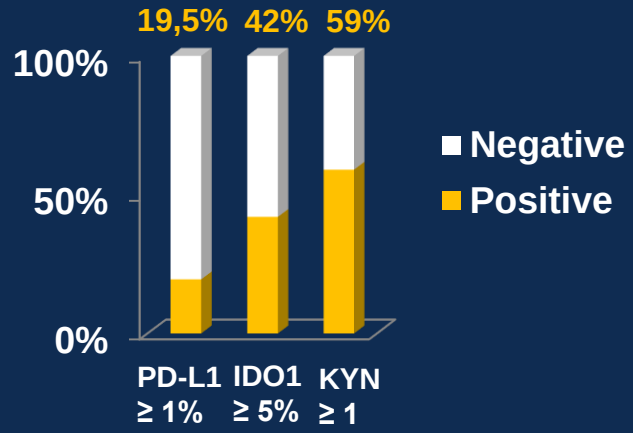
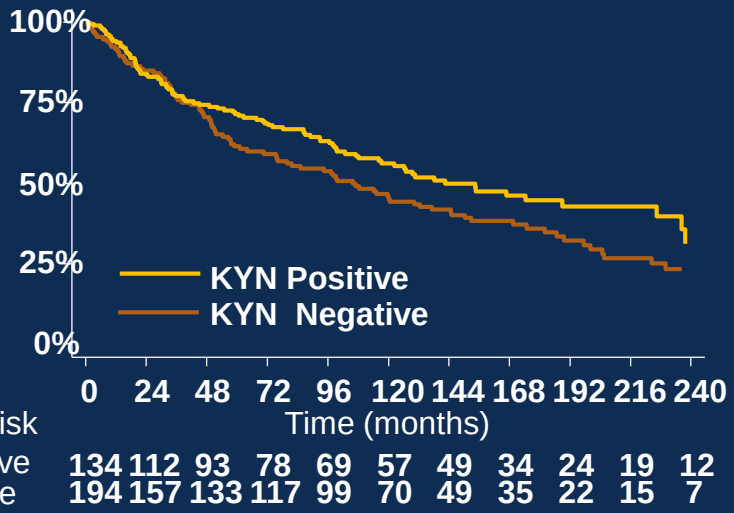
Abstract 3 – IDO1/KYN as potential biomarkers



Munn et al, Trends Immunol 2013





Number at risk											
KYN Negative	134	112	93	78	69	57	49	34	24	19	12
KYN Positive	194	157	133	117	99	70	49	35	22	15	7

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Optimizing Immunotherapy in Sarcoma

- If most sarcomas are not inherently immunogenic, can we induce it?
  - Chemotherapy, radiation, tyrosine kinase inhibitors, intratumoral injections, epigenetic agents?
- Identify and target immunogenic subtypes through better understanding of biology and the immune microenvironment
  - Histology based? CTA-expressing sarcomas, MITF sarcomas (alveolar soft part sarcoma, clear cell sarcoma), inflammatory subtypes, high genetic complexity?
- Target multiple mechanisms of immune evasion
  - Vaccine + checkpoint inhibitor + T-reg inhibitor?
  - TKI + IDO inhibitor?
- Take advantage of the extensive research ongoing in other cancers
  - New targets – new drugs – new models (immunoavatar mice)

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Ongoing Sarcoma Immunotherapy Trials

Vaccines	DC Vaccines	Adoptive T Cell Therapy
• **JX 595** (OV) + Cytoxan (Treg) • **Vigil** (FANG, autologous tumor vaccine) • PD-L1 inhibitor +/- **CMB305** (NY-ESO viral vector)	• Autologous **DC** (Miami, Spain) • Allogeneic **DC** (Russia) • **Intuvax** + sunitinib (GIST)	• **Tumor specific CD4** + ipi + Cytoxan (MDACC) • **NY-ESO-1 engineered TCR** for synovial, Myxoid/round cell LPS (Adaptimmune, Seattle) • **Her2 CAR T cells** for Her2+ sarcoma (Baylor)
Checkpoint Inhibitor Combinations		**Others!**
• Ipilimumab + nivolumab (Alliance) • Axitinib + pembrolizumab (Miami) • Pembrolizumab + cytoxan	• Pembrolizumab + gemcitabine/docetaxel	• TLR4 agonist + radiation (Seattle)

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Conclusions

- Checkpoint inhibitor therapy is likely to be effective strategy for a subgroup of patients
  - ? Immunoactive phenotype described by T cell infiltration, IDO/KYN expression, PD-1/PD-L1 expression?
  - Additional biomarker/ immunocorrelative studies are critical for future trials to further delineate immunoactive sarcoma
- Like chemotherapy and targeted therapies, combinations may be a more effective strategy – consistent with other solid tumors
- Off-label monotherapy probably ill-advised for most histologies but these results support enrollment in combination trials particularly for dedifferentiated LPS and UPS

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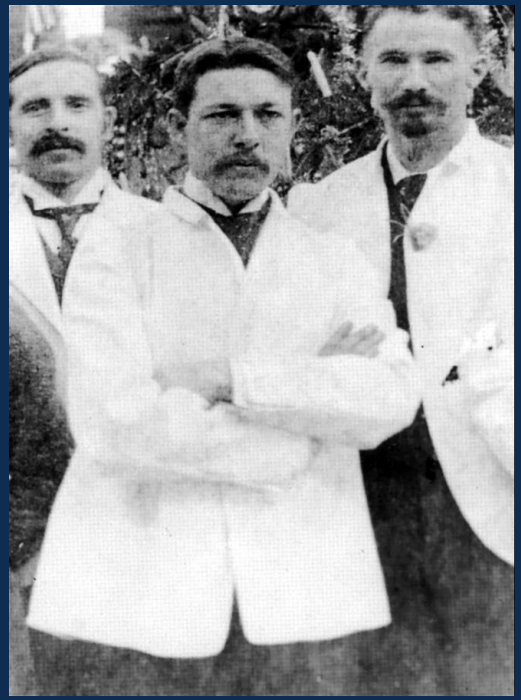

There is a future for immunotherapy in sarcomas…

Breelyn Wilky, MD
b.wilky@med.miami.edu

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM