Immunotherapy in Sarcoma: Where Do We Go From Here?

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Timeline of Immunotherapy in Sarcoma

Presented by: Breelyn A. Wilky, MD
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1890s

1980 - 2005

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

- Vaccines
  - Autologous tumor cells
  - Dendritic cells
  - GVAX

2005 - 2012

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

2010 - today

- Checkpoint inhibitors

Wilky and Goldberg, Discov Med 2014
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
The Cancer Immunoediting Hypothesis

- Immunosurveillance
- Immunoediting
- Escape

Schreiber, Old, Smyth Science 2011
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
# Strategies for Immunotherapy

<table>
<thead>
<tr>
<th>Target</th>
<th>Therapeutic Strategy</th>
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<tbody>
<tr>
<td>Immunogenic tumor-specific antigens</td>
<td>Vaccines</td>
</tr>
<tr>
<td>Effective antigen presentation/recognition</td>
<td>DCs, oncolytic viruses, agonists</td>
</tr>
<tr>
<td>Antigen-specific T cell production</td>
<td>Adoptive T Cell therapy</td>
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<tr>
<td>Improve T cell localization within tumor</td>
<td>Microenvironment</td>
</tr>
<tr>
<td>T cell ratio effector &gt; anergic</td>
<td>Immunostimulatory receptors</td>
</tr>
<tr>
<td>Counteract immunosuppression</td>
<td>Checkpoint blockade, anti-Treg</td>
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Adapted from Jedd Wolchok and others
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
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%)
Abstract 1 – SARC 028 Pembrolizumab

- 3 patients with partial responses

**SARC 028 Progression-Free Survival: Bone Sarcomas**

- Ewings: 7 (7, 8) / 12 / 13
- Osteosarcoma: 8 (7, 10) / 17 / 21
- Chondrosarcoma: 14 (7, 20) / 5 / 6

**Change in Target Lesion Size**

- Bone Sarcomas

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

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

<table>
<thead>
<tr>
<th>IHC PDL1 % positive</th>
<th>IHC PD1 % positive</th>
<th>IHC PDL2 % positive</th>
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<tbody>
<tr>
<td>malignant cells</td>
<td>non-malignant cells</td>
<td>malignant cells</td>
</tr>
<tr>
<td>7 0 NA</td>
<td>0 NA</td>
<td>90 na</td>
</tr>
<tr>
<td>9 0 20</td>
<td>0 0</td>
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<td>40 0</td>
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<tr>
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<tr>
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<td>20 0</td>
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<tr>
<td>5 20 0</td>
<td>0 5</td>
<td>90 0</td>
</tr>
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Abstract 3 – IDO1/KYN as potential biomarkers

Munn et al, Trends Immunol 2013

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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)
Ongoing Sarcoma Immunotherapy Trials

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<th>Vaccines</th>
<th>DC Vaccines</th>
<th>Adoptive T Cell Therapy</th>
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</table>
| • **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) |

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<th>Checkpoint Inhibitor Combinations</th>
<th>Others!</th>
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| • Ipilimumab + nivolumab (Alliance)  
• Axitinib + pembrolizumab (Miami)  
• Pembrolizumab + cytoxan | • Pembrolizumab + gemcitabine/docetaxel |
| | • TLR4 agonist + radiation (Seattle) |
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...