New Tumor Immunotherapy Strategies on the Horizon: Adoptive Cell Therapy for Metastatic Melanoma

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Conflict of Interest

• None
Outline

• Tumor-Infiltrating Lymphocyte (TIL) Cell Therapy: introduction and preliminary clinical trial results

• Methods to improve TIL Cell Therapy
  ➢ 4-1BB agonistic antibody *in vitro*
  ➢ PD-1 abrogating antibody *in vivo*
The Cure for Cancer (in mice)
Tumor immunity in mice is mediated by T lymphocytes
Tumor-Infiltrating Lymphocytes (TIL) Adoptive Cell Therapy

- TIL can be expanded *in vitro* and adoptively transferred as a treatment for metastatic melanoma
- Preparative chemotherapy and post transfer high dose bolus IL-2
- 56% Objective Response Rate (treated patients)
  22% Complete Response Rate (treated patients)
  CRs: 93% 5 year survival *unrivaled results
  Rosenberg, et al. CCR 2011
- Expensive, technically challenging, toxic
Moffitt’s TIL Trial for Unresectable Melanoma

Harvest Melanoma ≥ 2 cm

Plate Tumor Fragments for TIL in IL2

1. Grow for 3-5 weeks (Target ~30 to 50 Million TIL)

2. Rapid Expansion (2 weeks, 500-1000 fold expansion)

Digest (Tumor Cell Targets)

HLA-Restricted IFNγ ELISA Specificity Assay

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Rapid Expansion

30-60 bags required
Patient Clinical Result

Pre TIL | 2 MONTHS POST | 24 MONTHS POST

02/03/11 | 04/07/11 | 02/07/13
1.6 x 1.5 cm | 0.8 x 0.6 cm | 0 cm

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Pretibial Melanoma Metastasis

1.8 x 1.1 cm  1.5 x 0.9 cm  0 x 0 cm

* Of note, the patient came off pain medications previously required for leg pain.
Lower Jaw Metastasis

PRE

4 MONTHS POST

2.4 x 2.2 cm

0.9 x 0.5 cm
Visceral Metastasis

PRE

11 MONTHS POST

2.8 X 6 cm

0 X 0 cm
Symptomatic Arm Lesion

Pre

8 Days Post
Example of Prolonged Stable Disease

Pre-TIL 
12/13/2010
2.1 x 3.0 cm

27 months Post 
3/26/2013
2.0 x 1.5 cm

Pre-TIL 
12/13/2010
2.6 x 1.7 cm

27 months Post 
3/26/2013
1.7 x 1.3 cm
Moffitt ACT Clinical Results Summary

- 13 of 20 (65%) enrolled patients were successfully treated
- 4 (20%) enrolled patients dropped out prior to treatment due to progression
- 3 (15%) dropped out due to other reasons
- 3 (23%) had Complete Responses
- 6 (46%): Progression-Free Survival > 1 yr

Current direction: Immunomodulatory antibodies to accelerate TIL growth and improve anti-tumor efficacy

Pilon-Thomas et al., J Immunother 2012
4-1BB Agonistic Antibody Increases TIL Expansion *in vitro*

- *p* = 0.001, *n* = 7
4-1BB Ab Enhances HLA-Restricted, Tumor-Specific Cytokine Release

* p = 0.05
4-1bb Agonistic Antibody Summary

• Enhances TIL numbers

• Enhances CD8+ effector T cell phenotype

• Enhances tumor-induced IFN-γ production
PD1 Blockade: Reviving Exhausted T Cells

T cell exhaustion

T cell

TCR

PD1

HLA

PDL1

Tumor

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PD1 Blockade: Reviving Exhausted T Cells
Aim

• To determine if a PD-1 abrogating antibody *in vivo* prior to tumor harvest may increase resulting CD8+ TIL and tumor-specific IFN-γ production
PD-1 Blockade *in vivo* Prior to TIL Harvest Augments Adoptive Cell Therapy in a Murine B16 Model

* p < 0.05

![Graph showing CD8+ T cells and IFN-γ levels](image)
Combination of αPD-1 *in vivo* and 4-1BB *in vitro* Enhances Anti-Melanoma Reactivity

![Graph showing IFN-γ release](image)

* p<0.001
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