Chimeric Antigen Receptor T Cell Therapies for Advanced Prostate Cancer
Clinical Trials (and Tribulations)

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OBJECTIVES

- REVIEW CURRENT MECHANISMS AND RATIONALE FOR RE-DIRECTED T CELL THERAPIES FOR ADVANCED PROSTATE CANCER
- DESCRIBE AN EARLY EXPERIENCE WITH CAR-T THERAPY FOR ADVANCED PROSTATE CANCER
- DISCUSS CHALLENGES AND FUTURE APPROACHES FOR PROSTATE CANCER CAR-T THERAPY
Complexity of Immune Oncology Targets in Advanced Cancer

Other checkpoints: PD-1/PD-L1, CTLA-4, OX40, LAG-3, Tim3,..
Engineered T-Cell Therapy: CARs, BiTEs, TCRs, and more

- Immunotherapy aims to induce anti-tumor response by “active” or “passive” means:
  - Augmenting immune surveillance and cytotoxicity
  - Reducing immune suppression

- Native tumor-specific T cell repertoire is generally limited and low affinity (central tolerance)

- T cell Engineering boosts the immune system’s natural recognition abilities through genetic manipulation

Chimeric antigen receptor Structure

Extracellular Domain:
• Target recognition
• scFv of a monoclonal antibody

Hinge Region:
• Spacer providing flexibility

Costimulatory Domain(s):
• Enhancing cytotoxicity
• Derived from CD28, 4-1BB

Activation Domain:
• Initiating cytotoxicity
• Cytoplasmic motif from CD3z
**High Response Rates in Refractory Acute Lymphoblastic Leukemia**

Durable remission associated with T cell Intrinsic Factors:

- Increased peak expansion of CAR T cells and long persistence
- Cell products demonstrating greater proliferative capacity *ex vivo*
- Phenotypic signatures of early memory differentiation (versus terminal differentiation/exhaustion in Non-Responders)

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**CART cells for ALL: phase I/II trials:**

- Maude, Grupp *NEJM* 2018 82% CR 3 months
- Park *NEJM* 2018 83% CR 3 months

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Challenges for CAR T Cell Therapy in Solid Tumors

• In experience to date, clinically meaningful responses are rarely observed.

• Anti-tumor potency limited by:
  • Lack of substantial expansion and/or survival of CAR T cells
  • Tumor Microenvironment (Immunosuppressive, Physical Barriers)
  • Antigen Loss / Heterogeneity
  • On-Target / Off-Tumor Toxicity

Prostate Specific Membrane Antigen (PSMA)

- Membrane glycoprotein – evaluated as a tumor-associated antigen for >30 years
- Highly expressed in both normal prostate and PCa tissue
- High PSMA expression associated with PCa progression and castration-resistance
  - Expression increases with tumor grade
<table>
<thead>
<tr>
<th>Target Antigen: PSMA vs CD-19</th>
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<tbody>
<tr>
<td><strong>PSMA</strong></td>
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<tr>
<td>High / Universal Tumor Expression</td>
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<tr>
<td>Limited Normal Tissue Expression</td>
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<tr>
<td>Functional Role in Tumor / Indispensable</td>
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<tr>
<td>Antigen-related toxicity concerns</td>
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<tr>
<td>Low level Salivary, Renal, Intestinal</td>
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<td>?? Folate metabolism</td>
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<td>Normal B cells</td>
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<td>Hypogammaglobulinemia</td>
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</table>

Transforming Growth Factor β (TGFβ)

- Contributes to immunosuppressive microenvironment encountered by re-directed T cells upon tumor infiltration
  - Negative feedback of T cell proliferation
  - Limits T cell-mediated autoimmunity
- Co-expression of dominant negative TGFβRII can enhance anti-tumor immunity
Chimeric antigen receptor Structure

Extracellular Domain:
- Target recognition
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**Chimeric antigen receptor Structure**

- **Extracellular Domain:**
  - J591 scFv for PSMA target Ag

- **Hinge Region:**
  - Spacer providing flexibility

- **Costimulatory Domain(s):**
  - 4-1BB

- **Activation Domain:**
  - CD3z

"Armoring" with co-expression of a dominant negative TGFβ receptor (TGFβRdn) to enhance antitumor immunity

Follow-up every 3 months until 2 years; long term follow up until 15 years

Confirm mCRPC and tumor PSMA expression

Study screening, apheresis, T cell manufacture, disease staging

CART cell infusion 1-3 x 10^7/m^2

CART cell infusion 1-3 x 10^8/m^2

CART cell infusion 1-3 x 10^8/m^2

Cy 300 mg/m^2 + Flu 30 mg/m^2 x 3 days

Day 0

Days 1

3

7

10

14

21

Day 28

CT c/a/p staging, bone scan research studies, PSA

Month 2

Safety and research PSA

Month 3

CT c/a/p staging, bone scan research studies, PSA

Month 6

CT c/a/p staging, bone scan research studies, PSA

Follow-up

* Enrollment follows in succession from Cohort 1 to Cohort 3
Clinical Apheresis & Pre-Infusion Product Analysis

- T cell Differentiation Phenotype in Apheresis Product showed donor variability (left)

- Frequencies of expanded patient CD3+CD45+ T cells in Infusion Product expressing anti-PSMA CAR (median 65%) and TGFbRDN (median 19%) (center)

- Expression of TGFbRDN on manufactured PSMA-targeted CAR-T cells potently inhibited TGFb signaling through Smad2/3 phosphorylation (right)
Summary of Initial Cohorts (without LD chemotherapy)

- No evidence of CAR T cell activity in Cohort 1
  - No related Adverse Events
  - Little cytokine activity (Figure Inset)

- Evidence of anti-tumor CAR T cell activity in Cohort 2
  - Grade 3 CRS within hours of CAR T cell infusion
  - Adverse events were reversible
  - Robust cytokine activity in patients with Gr3 CRS

Conclusions:
- CART-PSMA-TGFβRDN cells are safe at 3x10^8/m^2 CAR+ cells without conditioning chemotherapy.
- There is a dose dependent relationship with cytokine detection.
**Study Schema**

Confirm mCRPC and tumor PSMA expression

CART cell infusion
1-3 x 10^7/m²

CART cell infusion
1-3 x 10^8/m²

CART cell infusion
1-3 x 10^8/m²

Study screening, apheresis, T cell manufacture, disease staging

Cy 300 mg/m² + Flu 30 mg/m² x 3 days

Cohort 1*  →  CART cell infusion
           1-3 x 10^7/m²

Cohort 2  →  CART cell infusion
           1-3 x 10^8/m²

Cohort 3  →  CART cell infusion
           1-3 x 10^8/m²

* Enrollment follows in succession from Cohort 1 to Cohort 3

Day 0  →  Days 1  →  3  →  7  →  10  →  14  →  21

Day 28
CT c/a/p staging,
bone scan research studies, PSA

Month 2
Safety and research PSA

Month 3
CT c/a/p staging,
bone scan research studies, PSA

Month 6
CT c/a/p staging,
bone scan research studies, PSA

Follow-up every 3 months until 2 years;
long term follow up until 15 years

ClinicalTrials.gov Identifier: NCT03089203. PI: N. Haas.
Correlation between CART-PSMA-TGFβRDN expansion and PSA reduction

Grade 5 Toxicity

How to optimize therapeutic index?
**Study Schema**

- **Day 0:** Study screening, apheresis, T cell manufacture, disease staging
- **Day 28:** CT c/a/p staging, bone scan research studies, PSA

**CART cell infusion**
- **Cohort 1**: 1-3 x 10^7/m²
- **Cohort 2**: 1-3 x 10^8/m²
- **Cohort 3**: 1-3 x 10^8/m²

**Confirm mCRPC and tumor PSMA expression**

**Safety and research PSA**

**Follow-up**
- Days 1, 3, 7, 10, 14, 21
- Follow-up every 3 months until 2 years; long term follow up until 15 years

**Cy 300 mg/m² + Flu 30 mg/m² x 3 days**

ClinicalTrials.gov Identifier: NCT03089203. PI: N. Haas.
CAR-T peak expansion increased with dose-escalation and incorporation of Cy / Flu LD chemotherapy
Higher grade CRS was associated with a greater magnitude of fold change in pro-inflammatory analytes post-infusion.
Preliminary Evidence for Dose-Dependent and LD-Chemo Dependent Anti-Tumor Response
CART-PSMA-TGFβRDN-02: A Phase 1 Open-Label Multi-Center Study of PSMA Targeted Genetically Modified Chimeric Antigen Receptor T-cells in Patients with Metastatic Castration Resistant Prostate Cancer

Current Study Schema

Completed cohort
No dosing occurred in cohort
Cohort to be initiated

Cohort 5
5-7 x 10⁶ TDN cells
Single infusion

Cohort 5a

Biotech

Tmunity stops solid tumor CAR-T trial after 2 patients die

Cohort 1
1.3 x 10⁶ TDN cells
Single infusion
N=2
Process 1

Cohort 2
5-7 x 10⁶ TDN cells
Single infusion

Cohort 3a
7-10 x 10⁶ TDN cells
Single infusion
N=3-6
Process 2

Use of prophylactic anakinra in applicable cohorts

Lymphodepleting Chemotherapy (D-6 to D-4)
- Cyclophosphamide 300 mg/m² x3-days
- Fludarabine 30 mg/m² x3-days
<table>
<thead>
<tr>
<th>Trial</th>
<th>Target</th>
<th>Sponsor</th>
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<tr>
<td>Phase 1 Study of CART-PSMA-TGFβRDN in Patients With Metastatic Castration Resistant Prostate Cancer</td>
<td>PSMA</td>
<td>Tmunity Therapeutics</td>
<td>NCT04227275</td>
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<td>Phase 1/2 Study of PSCA-Targeted CAR-T Cells (BPX-601) in Subjects With Selected Advanced Solid Tumors</td>
<td>PSCA</td>
<td>Bellicum Pharmaceuticals</td>
<td>NCT02744287</td>
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<td>P-PSMA-101 CAR-T Cells in the Treatment of Subjects With Metastatic Castration-Resistant Prostate Cancer (mCRPC)</td>
<td>PSMA</td>
<td>Poseida Therapeutics</td>
<td>NCT04249947</td>
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<td>PSCA-CAR T Cells in Treating Patients With PSCA+ Metastatic Castration Resistant Prostate Cancer</td>
<td>PSCA</td>
<td>City of Hope</td>
<td>NCT03873805</td>
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Challenges for CAR T Cell Therapy in Solid Tumors

Scientific Challenges:
- CAR Expansion/Survival
- Tumor Microenvironment
- Antigen Heterogeneity/Loss
- On-Target / Off-Tumor Effects

Clinical Challenges:
- Patient Selection
- Safety / Toxicity
- Therapeutic Window
Challenges for CAR T Cell Therapy in Solid Tumors

**Tumor Microenvironment**
- “Armoring” strategies – IL-12, IL-18, CD40L
- Dominant-Negative Receptors (dnTGFβRII, PD1)
- PD1 / CD28 “switch” receptors
- Combination Treatment Strategies (low dose RT)

**CAR Persistence / “Exhaustion”**
- Serial dosing strategies
- Novel inducible co-activation switches
- Immune checkpoint inhibitor adjuvants
- CRISPR-Cas9 editing (PD1 / LAG3)

**Antigen Selection / Targeting**
- Combination TAA scFvs
- Conditional activation switches
- Antigen spread

**Scientific Challenges:**
- CAR Expansion/Survival
- Tumor Microenvironment
- Antigen Heterogeneity/Loss
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...
Challenges for CAR T Cell Therapy in Solid Tumors

Clinical Challenges:
- Patient Selection
- Safety / Toxicity
- Therapeutic Window
Conclusions:

- Adoptive Cell Therapy with CAR-Modified T Cells is a transformative treatment for refractory cancers
- Multiple Tumor and Host factors will influence efficacy for prostate cancer CAR therapy
  - T cell potency / persistence
  - Antigen Heterogeneity
  - Tumor Microenvironment
  - Off-tumor Effects
- Rational combination / multifunctional approaches are needed
- Enhanced toxicity mitigation strategies remain critical for optimal Risk : Benefit (first in human trials)