T Cell Receptor Gene Therapy for Cancer

Let Every Woman Know
2022 Gynecologic Cancer Awareness & Arts of Healing Weekend

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Conflict of Interest Statement

• Patents and royalties: multiple NIH patents in cell therapy and immunotherapy with blinded royalty payments
• Research funding: Kite Pharma (past), T-Cure Biosciences, Neogene Therapeutics
• Consulting: GlaxoSmithKline, PACT Pharma
• All drug information is experimental and off-label
Engineered T Cell Therapy

- Success with CAR-T cells in hematologic cancers
- *Progress in epithelial cancers has been difficult and more research is needed*
Research Goals

• Short-term: Investigate principles of cellular therapy in epithelial cancers using HPV-associated cancers as a disease model.

• Long-term: Discover and develop cellular therapies for HPV-associated cancers and other malignancies.
TCRs Versus CARs

CAR: Cell surface target
- T cell
- Chimeric antigen receptor
- Cell surface protein
- 11% of protein-coding genes

TCR: Any target
- T cell
- T-Cell receptor
- Peptide
- HLA
- β2-microglobulin
- Target Protein
- Proteasome
- Peptide
- TAP
HPV-Associated Epithelial Cancers
Research Rationale

• Unmet clinical need

• Attractive therapeutic targets

• Unique research opportunities
HPV-TIL Treatment

- ORR 7/29; 2 durable CRs
- Development by Iovance Biotherapeutics (LN-145)
Complete Regression of Metastatic Cervical Cancer

Patient 3
• 36 year-old woman
• Squamous cell carcinoma (HPV-16+)
• Bleomycin, vincristine, cisplatin
• Cisplatin, gemcitabine + radiation
• Topotecan, paclitaxel

Stevanović, J Clin Oncol, 2015
Complete Regression of Metastatic Cervical Cancer

Patient 6

- 36 year-old woman
- Adenocarcinoma (HPV-18+)
- Cisplatin + radiation
- Refractory primary tumor
- Extrapelvic progression

Baseline vs. 20 Months
E6 TCR-T Cell Treatment

- ORR 2/12
- Tumor intrinsic immune-related genetic defects
E7 TCR-T Cell Treatment

- Higher avidity TCR
Trial Design

• First-in-human, Phase I, 3+3 dose escalation

• E7 TCR gene engineered T cells (E7 TCR-T cells)

• Metastatic HPV-16+ cancer, HLA-A*02:01 allele

• Any prior treatment, including checkpoint

• E7 TCR-Ts
  – DL1:  $1 \times 10^9$  E7 TCR-T cells
  – DL2:  $10 \times 10^9$  E7 TCR-T cells
  – DL3:  $100 \times 10^9$  E7 TCR-T cells
Treatment Schema

- Cyclophosphamide 30 or 60 mg/kg
- Fludarabine 25 mg/m²
- Aldesleukin 720,000 IU/KG
- E7 TCR-T cells
### Patient and Treatment Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Primary Tumor</th>
<th>Metastatic Disease Sites</th>
<th>Prior Systemic Agents</th>
<th>Prior PD-1 checkpoint</th>
<th>E7 T cells/CD3 T cells (%)</th>
<th>Response (duration in months)*</th>
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*Duration is measured in time from E7 TCR-T cell infusion. Patient 7 and Patient 8 had unconfirmed responses.

Nagarsheth, Nat Med, 2021
Patient 1

- 49-year-old female with vulvar cancer
- Prior treatment with 7 systemic agents
- Extensive lung, retroperitoneal, pelvic, and thigh metastases
- 8-month response

Nagarsheth, Nat Med, 2021
Patient 5

• 59-year-old male with anal cancer
• 3 prior systemic agents
• Prior pembrolizumab (PD-1 blockade)
• Lung, bone, and kidney metastases
• 9-month response

Nagarsheth, Nat Med, 2021
Patient 12

• 40-year-old female with cervical cancer
• 7 prior systemic agents
• Prior atezolizumab (PD-L1 blockade)
• Soft tissue, retroperitoneal, and rectal metastases
• 8-month response
Peripheral Blood Engraftment of E7 TCR-T cells

Nagarsheth, Nat Med, 2021
Reactivity of Peripheral Blood T cells against E7

Nagarsheth, Nat Med, 2021
Mechanism of Resistance: Defects in HLA-A*02:01 and B2M

- HLA-A*02:01/B2M defects in treatment-resistant tumors from 3 of 4 patients

Nagarsheth et al, Nat Med, 2021
E7 TCR-T Cell Summary

- Dose not limited by toxicity
- Responses include complete regression of many tumors, bulky tumors, and PD1/PDL1-refractory tumors
- High engraftment of functional engineered T cells
- HLA and B2M represent conspicuous biomarkers
- Phase II trial is ongoing at NIH and will be starting at Rutgers Cancer Institute
- An induction therapy trial for locoregionally advanced cancers is planned
Targeting KK-LC-1 for the Treatment Epithelial Cancers

Target (KK-LC-1)
- Restricted to germ cells
- Expressed by cancers
  - Gastric 81%
  - TNB 53%
  - NSCLC 40%

TCR
- HLA-A*01:01 restricted

Stevanovic, Science, 2017
KK-LC-1 TCR-T Cells Mediate Regression of Established Tumors in NSG Mice

Marcinkowski, J Immunother Cancer, 2019
KK-LC-1 TCR

- The KK-LC-1 TCR was the dominant TCR in the TIL that cured a patient with cervical cancer
- KK-LC-1 TCR-T cells mediate tumor regression in mice
- Phase I trials will be starting at NIH and Rutgers
Summary of Cell Therapy in Epithelial Cancers

• HPV-TIL have demonstrated safety and clinical activity
  • Proof-of-principle for a cell therapy in an epithelial cancer; durable, complete responses
  • In development by Iovance Biotherapeutics

• E7 TCR T cells have demonstrated safety and clinical activity
  • Proof-of-principle for engineered T cells in epithelial cancer
  • Phase II trial ongoing, induction therapy trial planned

• KK-LC-1 is a promising target for a range of common cancers

• Other efforts to watch
  • ADP-A2M4CD8 (MAGE-A4) in a range of tumors
  • Recent report of TIL therapy in lung cancer