Gene-Engineered T cell Therapy for HPV-Associated Diseases

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HPV-Associated Malignancies

• 42,000 new cases diagnosed each year
  • Incidence is rising
• Epithelial Cancers
  • Squamous cell carcinomas and adenocarcinomas
  • Cervix, oropharynx, anus, vulva, vagina, penis
  • Incurable in metastatic setting and difficult to palliate
Head and Neck Cancer

• Incidence of HPV-associated OPC risen 225% in past two decades
• EXTREME Regimen
  • Cisplatin + 5-FU + Cetuximab
  • RR 35%
  • Improved OS 7.4 to 10.1 months
• KEYNOTE-048
  • Pembrolizumab + platinum/5-FU in PD-L1+ disease
  • Improved OS 10.4 to 13.6 months
• 2\textsuperscript{nd}-line therapy
  • PD-1 based therapy RR 15-25%
  • Single agent chemo 10-20%
Cervical Cancer

- Worldwide, 4th most common cancer among women
- Results in 260,000 deaths worldwide per year
- Platinum-doublet chemotherapy
  - Platinum + Taxol/Vinorelbine/Gem/Topotecan
  - RR 20-40%
- Platinum-doublet chemotherapy + Bevacizumab
  - Improved OS 13.3 to 17 months
- 2nd-line therapy
  - PD-1 based therapy RR 10-20%
  - Single agent chemo 10-15%
Other HPV-Associated Malignancies

- 12,000 new cases of vaginal, vulvar, penile and anal cancer combined each year in US
- Platinum-doublet chemotherapy
  - Anal cancer treated with Cis + 5-FU
  - Vulvar/Vaginal with Carbo + Taxol
- PD-1 based therapy
  - RR 15-25%
T cell Therapy Target Antigens

- **Attractive therapeutic targets**
  - HPV E6 and HPV E7
    - Constitutively expressed antigens
    - Tumor-restricted
    - “Public” antigen
    - Intracellular (cannot be targeted with CAR T therapy or antibodies)
- **Target with intent to cure**
High-Risk HPV

- Immunotherapy Antigens
  - **L1**
    - Prevention vaccines
    - Major capsid protein (antibody)
    - Not consistently expressed by cancers
  - **E6/E7**
    - Cancer immunotherapy
    - Intracellular oncoproteins (T cell)
    - Constitutively expressed by cancers
TCR therapy:
- Tumor antigen endogenously processed and presented on MHC
- HPV-16 E7 protein (epitope 11-19) processed and presented in the context of HLA-A*02:01 on tumor cells
- E7 TCR recognizes E7 in the context of HLA-A*02:01
Treatment Schema

-7, -6, -5, -4, -3, -2, -1, 0, 1, 2, 3, 4

Cyclophosphamide 30 or 60 mg/kg

E7 TCR-Ts

Fludarabine 25 mg/m²

Aldesleukin 720,000 IU/kg
## Phase I E7 TCR T-cell Clinical Trial

### Table 1. Patient and treatment characteristics

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Sites of Disease</th>
<th>Prior Systemic Treatments</th>
<th>Cell dose (x10^9)</th>
<th>Cyclophosphamide dose (mg/Kg)</th>
<th>Aldes-leukin doses</th>
<th>Response (duration in months)*</th>
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<tbody>
<tr>
<td>1</td>
<td>49</td>
<td>F</td>
<td>Vulvar SCC</td>
<td>Cisplatin, topotecan, carboplatin, paclitaxel, bevacizumab, trametinib, erlotinib</td>
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<td>SD (3)</td>
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<tr>
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<td>F</td>
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<td>60</td>
<td>6</td>
<td>NR</td>
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<td>Anal SCC</td>
<td>Mitomycin, 5-FU, pembrolizumab</td>
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<td>Mitomycin, 5-FU, oxaliplatin, cisplatin, nivolumab</td>
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<td>Head and Neck SCC</td>
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<tr>
<td>11</td>
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<td>Cervical SCC</td>
<td>Cisplatin, paclitaxel, bevacizumab, pemetrexed, pembrolizumab</td>
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<td>30</td>
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<td>40</td>
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<td>Cervical SCC</td>
<td>Cisplatin, paclitaxel, bevacizumab, carboplatin, gemcitabine, atezolizumab, pemetrexed</td>
<td>100</td>
<td>30</td>
<td>1</td>
<td>PR (8)</td>
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</table>

* Duration is measured in the time from E7 T cell infusion.

**Treated with another agent without having progressed.

Abbreviations: F, female; M, male; SCC, squamous cell carcinoma; FU, fluorouracil; PR, partial response; SD, stable disease; NR, no response.
Complete Regression of Lesions

- 4/6 had complete regression of at least one lesion
- 3/6 had complete regression of multiple lesions
Patient 1

- 49-year-old female with vulvar cancer
- 7 prior systemic agents
- Multiple lung, abdominal, retroperitoneal, pelvic and thigh metastases
- 8-month partial response
Patient 5

- 59-year-old male with anal cancer
- 3 prior systemic agents
- Prior pembrolizumab
- Multiple lung, pleural, kidney and bone metastases
- 9-month partial response
Patient 12

- 40-year-old female with cervical cancer
- 7 prior systemic agents
- Prior atezolizumab
- Chest wall, rectal and retroperitoneal metastases
- 8-month partial response
## Table 1. Patient and treatment characteristics

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<th>Response (duration in months)*</th>
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<tbody>
<tr>
<td>1 61</td>
<td>M</td>
<td>Head and Neck SCC</td>
<td>Lung</td>
<td>Cetuximab, nivolumab</td>
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<td>60</td>
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<td>2 38</td>
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<td>Cervical SCC</td>
<td>Retroperitoneum, pelvis</td>
<td>Cisplatin, ipilimumab, paclitaxel, carboplatin, bevacizumab</td>
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<td>30</td>
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<td>SD (1†)</td>
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<tr>
<td>3 49</td>
<td>F</td>
<td>Cervical Adenocarcinoma</td>
<td>Abdomen, mesentery, inguinal</td>
<td>Cisplatin, carboplatin, paclitaxel, bevacizumab, DPX-E7 vaccine, cyclophosphamide, tisotumab vedotin</td>
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<td>30</td>
<td>1</td>
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<td>4 39</td>
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<td>Esophageal SCC</td>
<td>Retroperitoneum</td>
<td>Carboplatin, paclitaxel, docetaxel, cisplatin, 5-FU, pembrolizumab</td>
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<td>30</td>
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<tr>
<td>5 50</td>
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<td>Head and Neck SCC</td>
<td>Lung, mediastinum, subcarinal</td>
<td>Cetuximab, carboplatin, paclitaxel, nivolumab</td>
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<td>30</td>
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<td>SD(4)</td>
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<tr>
<td>6 49</td>
<td>M</td>
<td>Head and Neck SCC</td>
<td>Lung</td>
<td>Cetuximab</td>
<td>100</td>
<td>30</td>
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<tr>
<td>7 54</td>
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<td>Cervical SCC</td>
<td>Abdomen, mesentery</td>
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<tr>
<td>8 60</td>
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<td>Head and Neck SCC</td>
<td>Lung, mediastinum</td>
<td>Docetaxel, cisplatin, 5-FU, carboplatin, nivolumab, pembrolizumab, paclitaxel, cetuximab</td>
<td>100</td>
<td>30</td>
<td>3</td>
<td>SD(3)</td>
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*Duration is measured from time of E7 T cell infusion.
†Came off study without having progressed.

Abbreviations: F, female; M, male; SCC, squamous cell carcinoma; FU, fluorouracil; PR, partial response; SD, stable disease; NR, no response; uPR, ongoing unconfirmed partial response
Patient 3

- 49-year-old female with cervical cancer
- 7 prior systemic agents
- Prior DPX-E7 vaccine
- Multiple peritoneal metastases
- 10-month partial response
Patient 4

- 39-year-old male with esophageal cancer
- 6 prior systemic agents
- Prior pembrolizumab
- Multiple retroperitoneal metastases
- 7-month partial response
Summary of Phase I/II Data

• 10/20 partial responses
• 5/10 responses in PD-1-refractory disease
• Ongoing enrollment
Persistence of E7 T cells in Blood

Frequency of E7 TCR-T cells/CD3+ cells (%)

E7 TCR-T cells (cells/µL)

Baseline 25 50 75 100 200 300

Persistence of E7 T cells in Blood
Function of Engrafted E7 T cells

- IFN-γ (Baseline)
- IFN-γ (Posttreatment)
- E7 TCR-T cells (Baseline)
- E7 TCR-T cells (Posttreatment)

<table>
<thead>
<tr>
<th>Patient</th>
<th>IFN-γ (Baseline)</th>
<th>IFN-γ (Posttreatment)</th>
<th>E7 TCR-T cells (Baseline)</th>
<th>E7 TCR-T cells (Posttreatment)</th>
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</table>

Note: The graph shows the comparison of IFN-γ and E7 TCR-T cell levels before and after treatment for different patients.
Tumor-Intrinsic Resistance to E7 T cells
Tumor-Intrinsic Resistance to E7 T cells

Patient 3

Patient 4

Patient 5

Patient 12
Early Treatment with E7 TCR T cells

Healthy Tissue

- High grade CIN
- Vulvar HSIL

Metastatic Cancer

- Early Stage OPC
- Locally Advanced
  - OPC
  - Cervical
- E7 w/ tethered cytokines

Modified. Iacobuzio-Donahue Sequencing, Clin Can 2012
E7 TCR T-Cells Vulvar HSIL

- High-grade, premalignant condition of the vulva
- Vulva consists of the external female genitalia
- Treatment includes
  - Surgery (wide local excision, skinning vulvectomy)
  - Ablative therapy
  - Topical therapy (imiquimod, fluorouracil)
E7 TCR T-Cells Vulvar HSIL

- Phase II study
- Single IV infusion of 100 billion E7 TCR T-cells
- Eligibility
  - HPV-16+ vulvar HSIL, HLA-A*02:01
  - Measurable lesion(s) that are recurrent or cannot be resected w/o acceptable cosmetic or functional results
E7 TCR T-cells for High-Grade CIN

- Grade 2-3, premalignant condition of the cervix
- Very common
  - Incidence of 5% in US
- HPV 16 and 18 account for 60% of all high-grade CIN
- Standard therapy effective but increases risk of future obstetric complications
- Patients are young women of child-bearing potential
- Newer non-surgical treatments with therapeutic vaccines have shown modest efficacy
LEEP Procedure

Risks include:

- Infertility
- PPROM
- Preterm delivery
- 2nd trimester pregnancy loss
- Perinatal death

https://www.brooklyngynplace.com/leep-obgyn-physicians-downtown-brooklyn-nyc/
E7 TCR T-cells for High-Grade CIN

- Phase I, 3+3 dose escalation
- HPV16+ high-grade CIN (grade 2,3), HLA-A*02:01
- Treatment-naïve or refractory if prior treatment $\geq$ 3 months
- Intralesional injection of E7 TCR T-cells
  - DL1: $3 \times 10^8$ D0, $3 \times 10^9$ D31
  - DL2: $3 \times 10^9$ D0, D31
- Response at 3 months is histopathologic regression to CIN1 or normal
- Translational studies to look at somatic mutations and immune microenvironment
Induction E7 for Stage II/III OPC

- 16,000 cases/year HPV+ OPC in US with incidence rising
- 95% of cases caused by HPV16
- Stage I
  - Ipsilateral LNs <6 cm
- Stage II
  - Tumor >4 cm, contralateral or b/l LNs
- Stage III
  - Tumor invades local structure(s), LN >6cm

https://www.cancerresearchuk.org/
Induction E7 for Stage II/III OPC

- Induction treatments are given prior to definitive standard of care therapy
  - Reduce distant disease recurrence
  - De-intensify definitive therapies
  - Study tumor genomics and TME
- Chemoradiation effective but 20% and 35% of stage II/III patients die within 5 years
- Patients are young and experience life long morbidity affecting swallowing, speech, taste and mastication, and chronic pain
Common Side Effects from Radiation

- **Mucositis**
- **Skin Reactions**
- **Xerostomia**
Induction E7 for Stage II/III OPC

- Stage II/III HPV16+ OPC, HLA-A*02:01
- Treatment-naïve
- Conditioning regimen, E7 TCR T-cells (intravenous), systemic aldesleukin
- Primary end point is feasibility
  - Referred to standard of care therapy at time of best response
Neoadjuvant E7 for Stage I OPC

- Aim to convert unresectable or borderline resectable disease to resectable
  - Study tumor genomics and TME
- Standard therapy with surgery or definitive chemoradiation are similarly effective
- Surgery has decreased morbidity and patients with low risk disease avoid adjuvant radiation therapy
- Patients are typically young making long-term morbidity important
Neoadjuvant E7 for Stage I OPC

- Borderline Resectable or Unresectable Stage I HPV16+ OPC
- Treatment-naïve, HLA-A*02:01
- No chemotherapy or aldesleukin
  - Local injection of E7 TCR T-cells into primary tumor and/or clinically palpable lymph node(s)
- Primary endpoint is feasibility
  - Referred to standard of care 4 weeks after injection
Induction E7 for Locally Advanced Cervical Cancer

- 13,000 new cases diagnosed each year
- Standard therapy is chemoradiation +/- extended field radiation therapy +/- vaginal brachytherapy
- High risk of relapse where 90% of patients die of disease within 5 years
- Radiation can lead to GI, urologic, female reproductive tract, skeletal and vascular toxicities
- Aim is to reduce disease recurrence and de-intensify pelvic chemoradiation
Induction E7 for Locally Advanced Cervical Cancer

- Feasibility study
  - Toxicity delaying definitive tx
  - Increase in T and N stage
  - Chemo without getting cells
  - Dose reduction in chemoXRT
- Lead-in safety cohort
  - FIGO Stage IIIC-IVA
  - Stops if <3/5 patients are success
Clinical Program for HPV Disease

- Metastatic HPV+ cancers
  - E7 TCR T-cells phase II
- Locally advanced HPV+ cancers (OPC and cervical)
  - Induction therapy
- Early stage HPV+ cancers (OPC)
  - Local therapy
- HPV infections
  - HSIL
  - CIN
Membrane-Anchored Cytokines

- IL-15/21 or IL-12

Diagram:
- Cytokine
- Linker
- Anchor (B7.1 TM domain)
- Cytokine Receptor
Membrane-Anchored IL-15/21

NSG mice with CaSki

Benjamin Jin
## Expanding Cell Therapy Program

<table>
<thead>
<tr>
<th>TARGET</th>
<th>DISEASE</th>
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<tbody>
<tr>
<td>Hepatitis B</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>KK-LC-1</td>
<td>Epithelial cancer</td>
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<tr>
<td>EBV</td>
<td>EBV-associated malignancies</td>
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<td>CD20</td>
<td>B-cell malignancies</td>
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<td>B-cell malignancies</td>
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<tr>
<td>PAX5</td>
<td>B-cell malignancies</td>
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Summary

- Clinical activity demonstrated with TCR targeting HPV-associated cancers
- Resistance to treatment due to tumor-intrinsic defects
  - Tethered-cytokines and treatment of early stage disease may overcome this resistance
- Treatment protocols for early-stage HPV-associated diseases
- Expanding cell therapy program to include non-HPV-associated diseases