

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
- **2nd-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%**

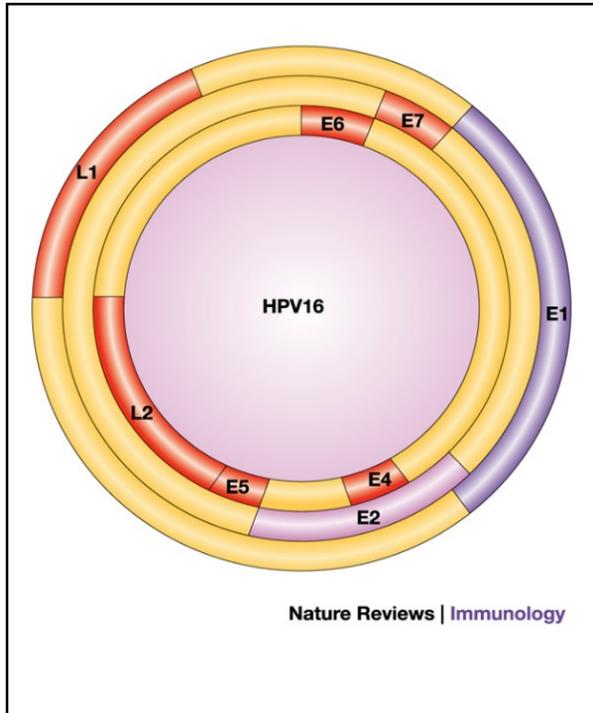
Other HPV-Associated Malignancies

- **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



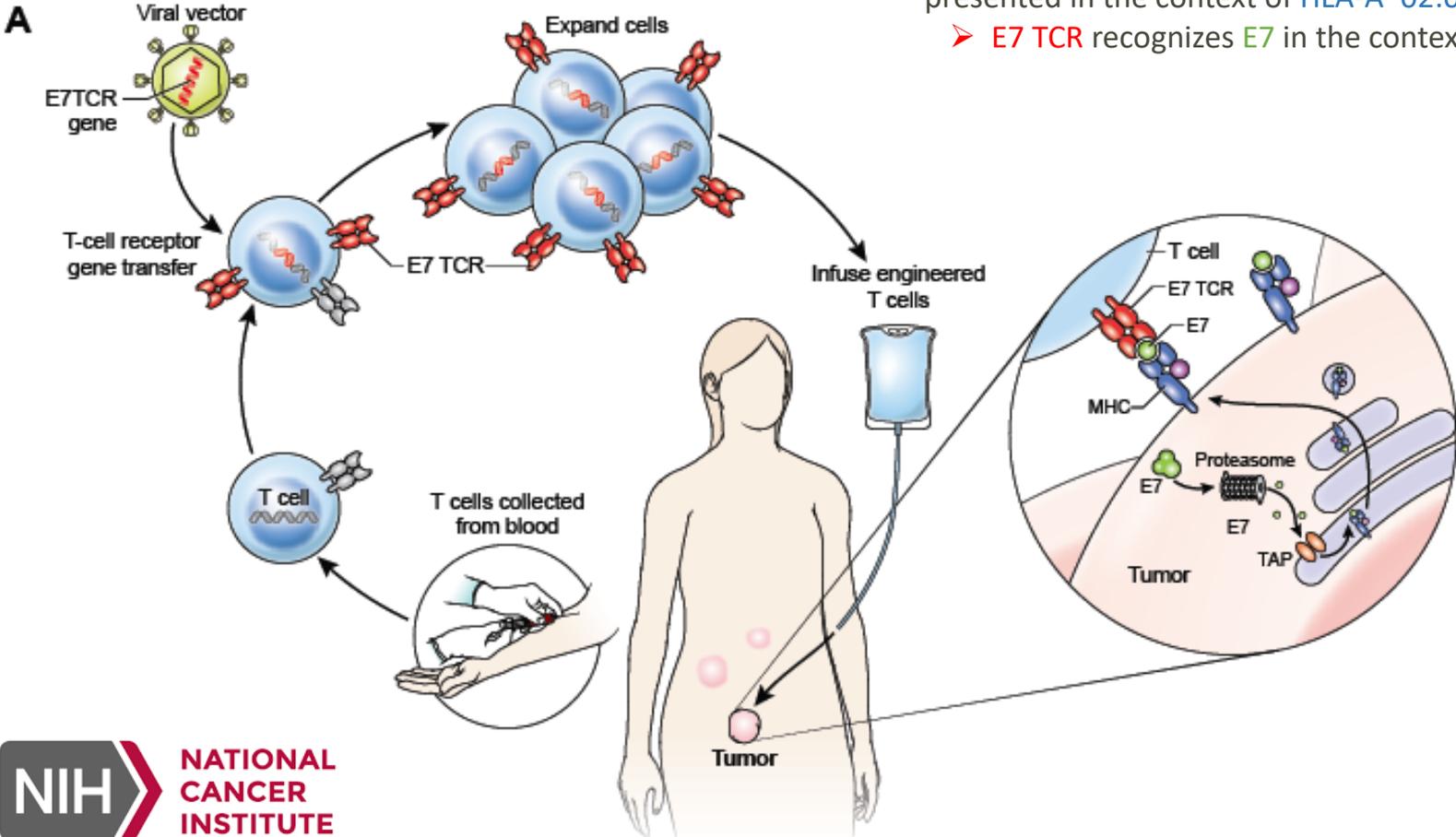
Immunotherapy Antigens

- **L1**
 - Prevention vaccines
 - Major capsid protein (antibody)
 - Not consistently expressed by cancers
- **E6/E7**
 - Cancer immunotherapy
 - Intracellular oncoproteins (T cell)
 - Constitutively expressed by cancers

E7 TCR T-cell Clinical Trial

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

Cyclophosphamide 30 or 60 mg/kg

E7 TCR-Ts

-7

-6

-5

-4

-3

-2

-1

0

1

2

3

4

Fludarabine 25 mg/m²

Aldesleukin 720,000 IU/kg

Phase I E7 TCR T-cell Clinical Trial

Table 1. Patient and treatment characteristics

	Age (years)	Sex	Diagnosis	Sites of Disease	Prior Systemic Treatments	Cell dose (x10 ⁹)	Cyclophosphamide dose (mg/Kg)	Aldes-leukin doses	Response (duration in months)*
1	49	F	Vulvar SCC	Lungs, mediastinum, retroperitoneum, pelvis, inguinal, thigh	Cisplatin, topotecan, carboplatin, paclitaxel, bevacizumab, trametinib, erlotinib	1	30	3	PR (8)
2	50	M	Head and Neck SCC	Kidney, bone	Cisplatin, pembrolizumab, nivolumab	1	60	10	SD (3 ^{**})
3	44	F	Cervical SCC	Inguinal, retroperitoneum	Cisplatin, carboplatin, paclitaxel, bevacizumab	1	30	10	SD (3)
4	44	F	Cervical SCC	Iliac, mediastinum, retroperitoneum	Cisplatin, paclitaxel, bevacizumab	10	60	6	NR
5	59	M	Anal SCC	Lungs, mediastinum, pleura, kidney, retroperitoneum, bone	Mitomycin, 5-FU, pembrolizumab	10	60	5	PR (9)
6	41	M	Head and Neck SCC	Bone, lung	Cisplatin, pembrolizumab, cetuximab, 5-FU	10	60	4	PR (4)
7	65	M	Head and Neck SCC	Lungs, abdominal wall, mediastinum, retroperitoneum, pleura, subdiaphragmatic, bone	Cisplatin, nivolumab, phase I drug, cetuximab, 5-FU, Lion TIL	100	30	6	PR (4)
8	31	F	Cervical Adenocarcinoma	Lungs	Cisplatin, paclitaxel, bevacizumab	107	30	3	PR (3)
9	62	F	Anal SCC	Liver, mediastinum, large intestine, lung	Mitomycin, 5-FU, oxaliplatin, cisplatin, nivolumab	107	60	3	SD (2)
10	59	M	Head and Neck SCC	Lung, mediastinum	Cisplatin, docetaxel, pembrolizumab, Cetuximab	120	60	3	SD (4)
11	40	F	Cervical SCC	Liver, lung, mediastinum, retroperitoneum, bone, pelvis	Cisplatin, paclitaxel, bevacizumab, pemetrexed, pembrolizumab	100	30	0	NR
12	40	F	Cervical SCC	Chest wall, rectum	Cisplatin, paclitaxel, bevacizumab, carboplatin, gemcitabine, atezolizumab, pemetrexed	100	30	1	PR (8)

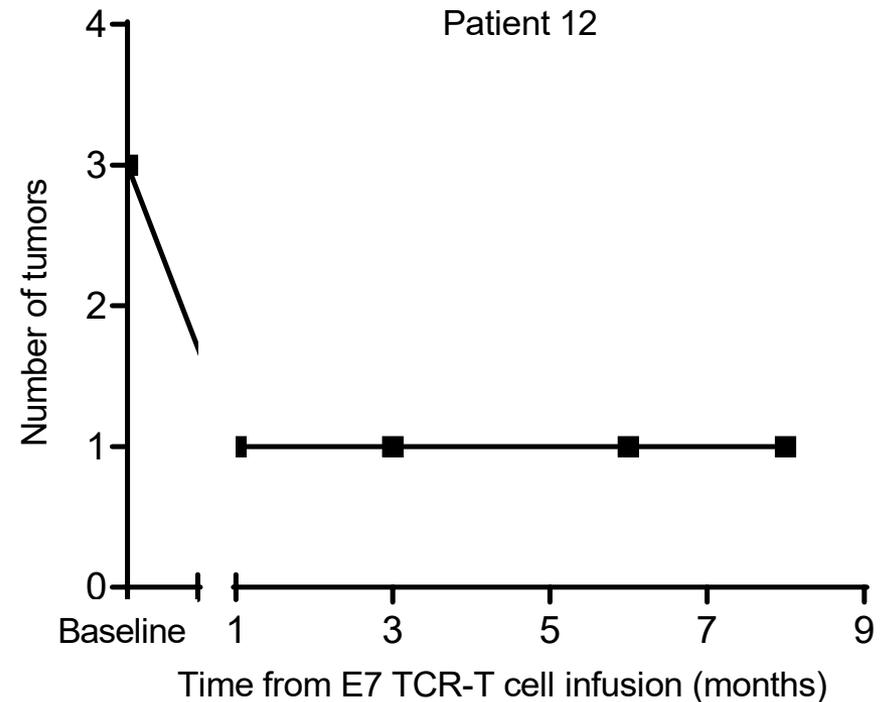
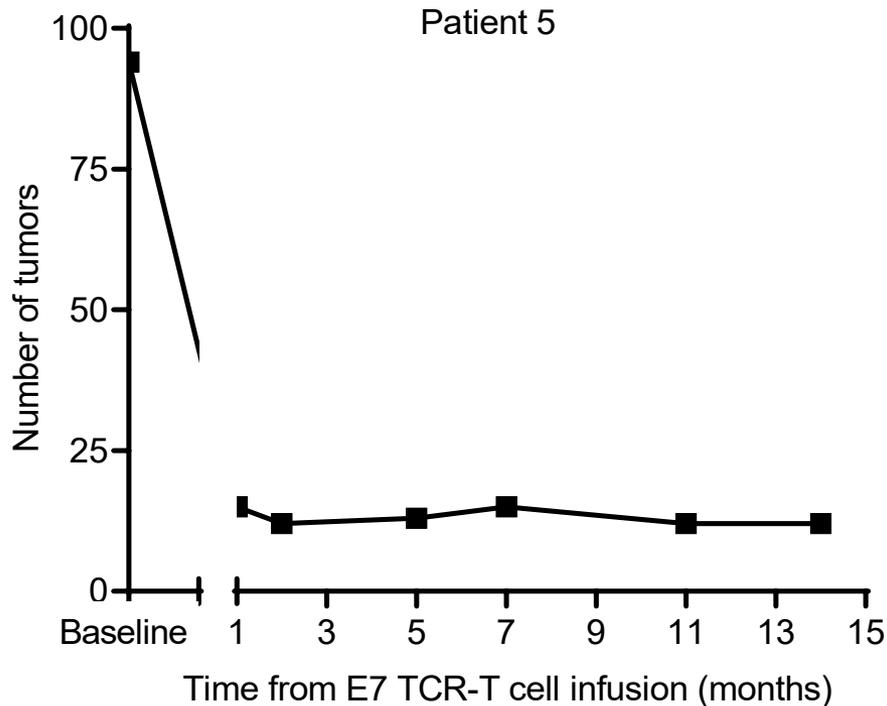
* Duration is measured in the time from E7 T cell infusion.

**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

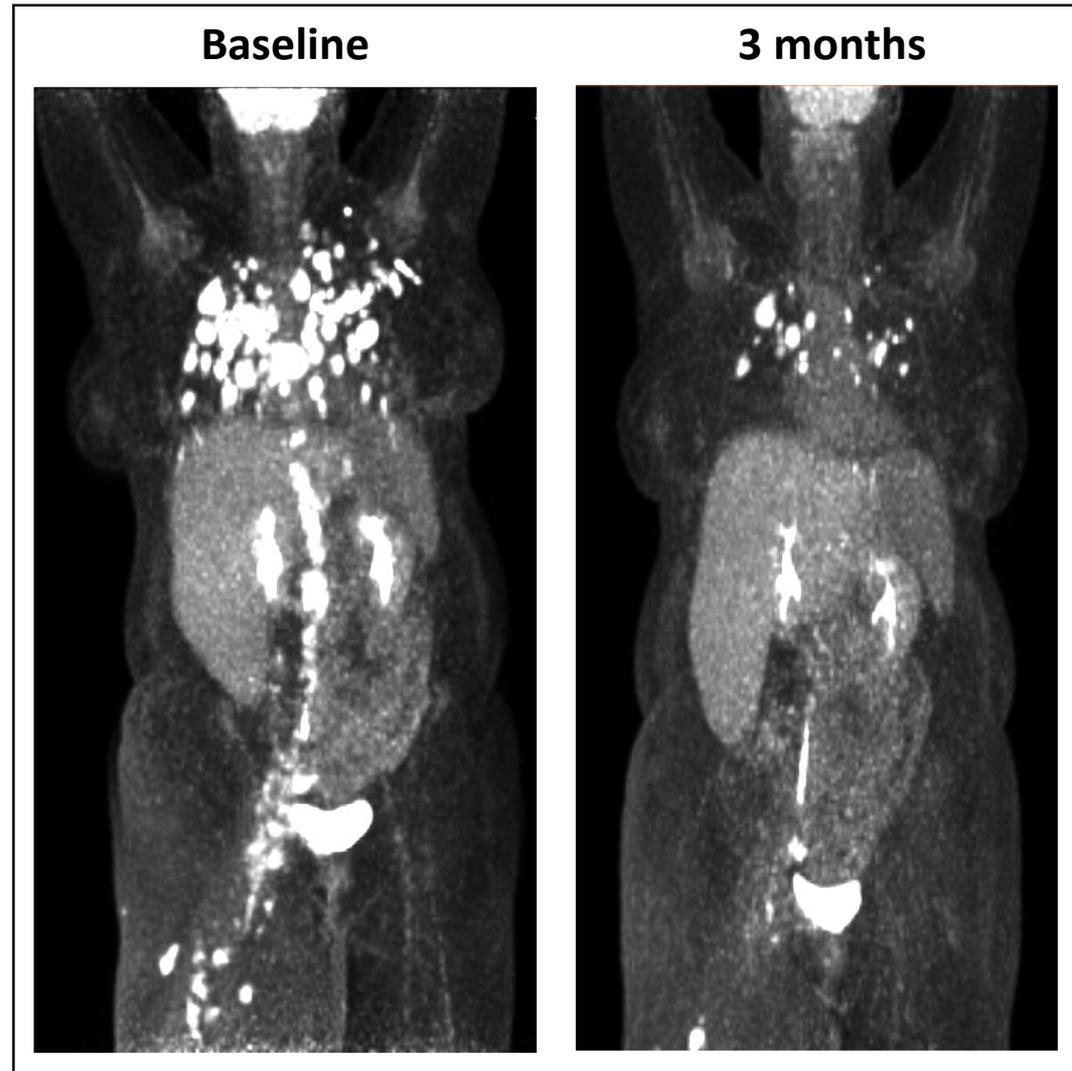
Complete Regression of Lesions

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



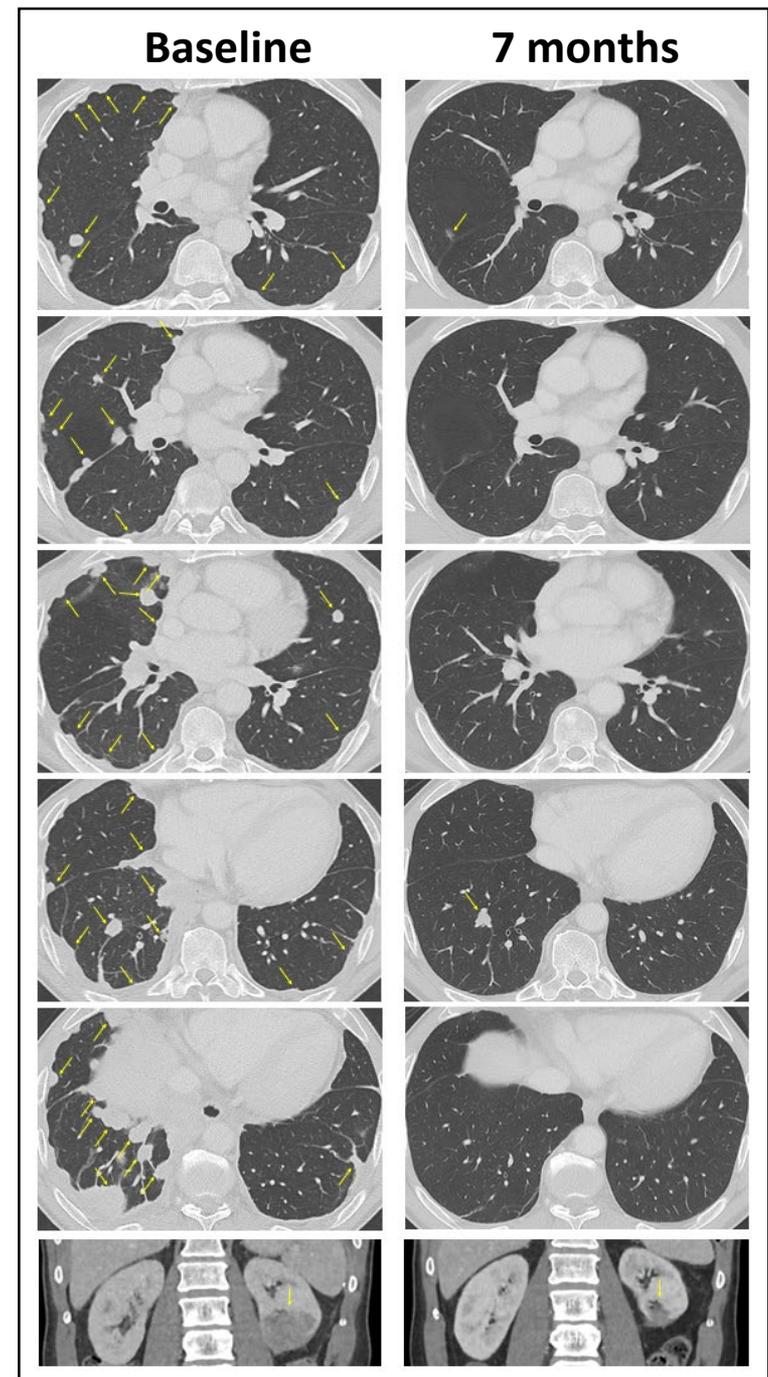
Patient 1

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



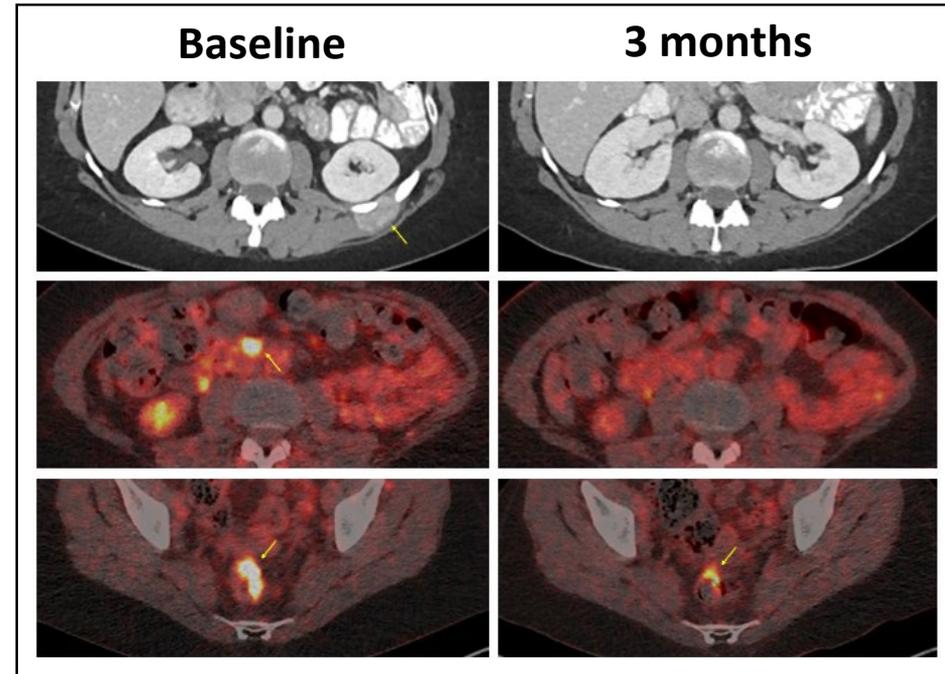
Patient 5

- 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



Phase II E7 TCR T-cell Clinical Trial

Table 1. Patient and treatment characteristics

	Age (years)	Sex	Diagnosis	Sites of Disease	Prior Systemic Treatments	Cell dose (x10 ⁹)	Cyclophosphamide dose (mg/Kg)	Aldes-leukin doses	Response (duration in months)*
1	61	M	Head and Neck SCC	Lung	Cetuximab, nivolumab	100	60	4	PR(6)
2	38	F	Cervical SCC	Retroperitoneum, pelvis	Cisplatin, ipilimumab, paclitaxel, carboplatin, bevacizumab	100	30	1	SD (1 [†])
3	49	F	Cervical Adenocarcinoma	Abdomen, mesentery, inguinal	Cisplatin, carboplatin, paclitaxel, bevacizumab, DPX-E7 vaccine, cyclophosphamide, tisotumab vedotin	100	30	1	PR(10)
4	39	M	Esophageal SCC	Retroperitoneum	Carboplatin, paclitaxel, docetaxel, cisplatin, 5-FU, pembrolizumab	100	30	2	PR(7)
5	50	F	Head and Neck SCC	Lung, mediastinum, subcarinal	Cetuximab, carboplatin, paclitaxel, nivolumab	100	30	2	SD(4)
6	49	M	Head and Neck SCC	Lung	Cetuximab	100	30	5	SD(1 [†])
7	54	F	Cervical SCC	Abdomen, mesentery	Cisplatin	100	30	2	PR(4)
8	60	M	Head and Neck SCC	Lung, mediastinum	Docetaxel, cisplatin, 5-FU, carboplatin, nivolumab, pembrolizumab, paclitaxel, cetuximab	100	30	3	SD(3)

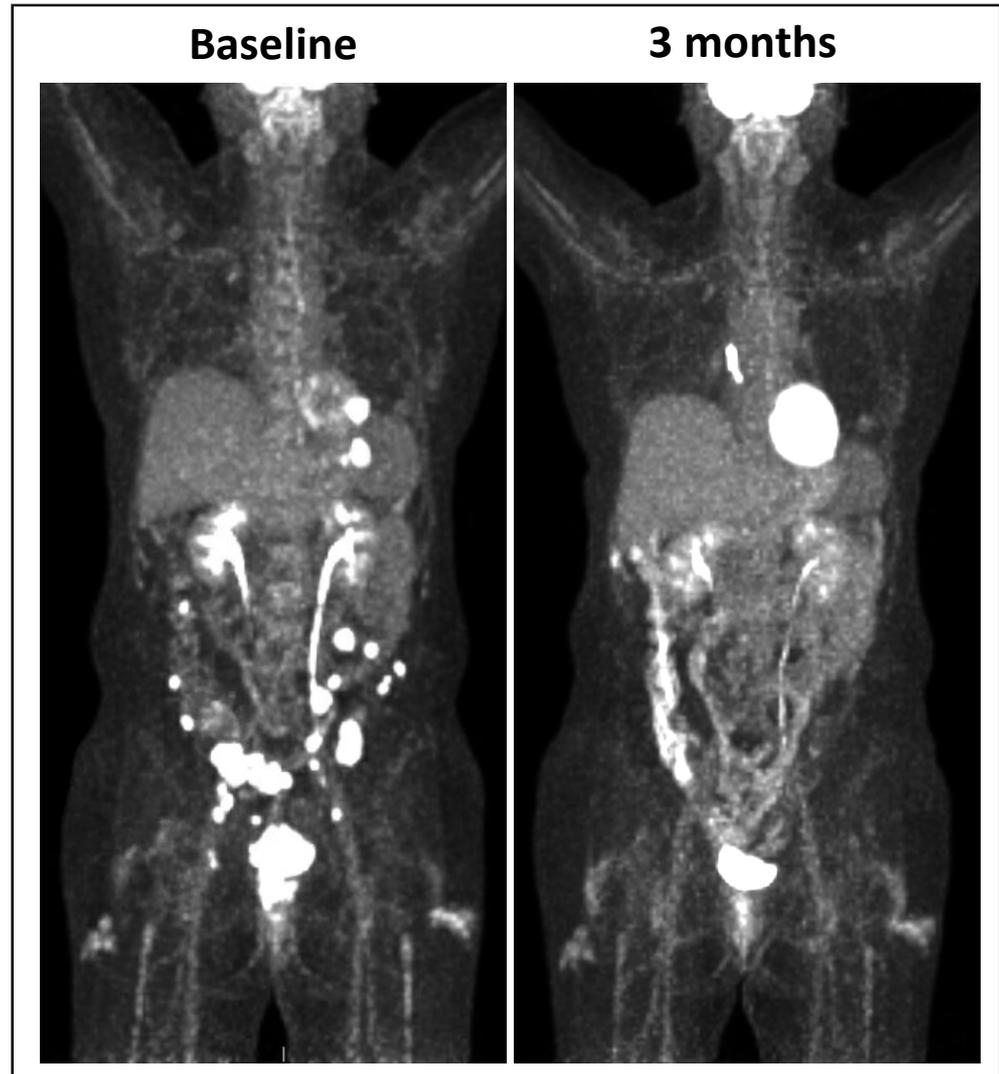
*Duration is measured from time of E7 T cell infusion.

[†]Came off study without having progressed.

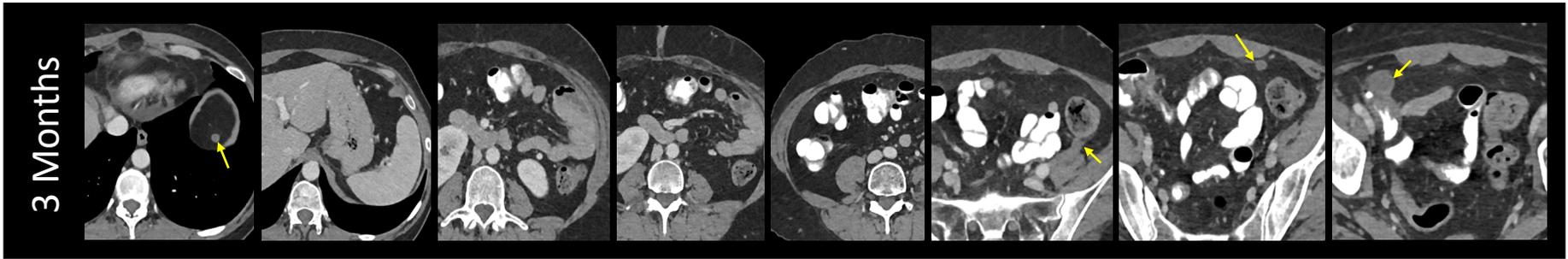
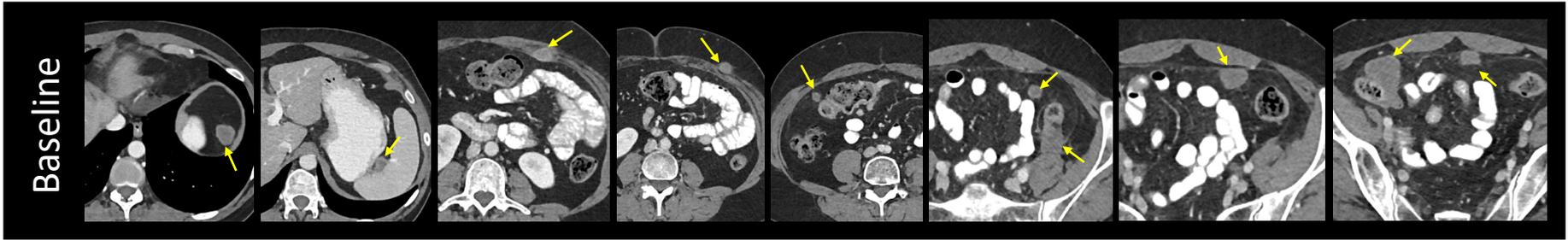
Abbreviations: F, female; M, male; SCC, squamous cell carcinoma; FU, fluorouracil; PR, partial response; SD, stable disease; NR, no response; uPR, ongoing unconfirmed partial response

Patient 3

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

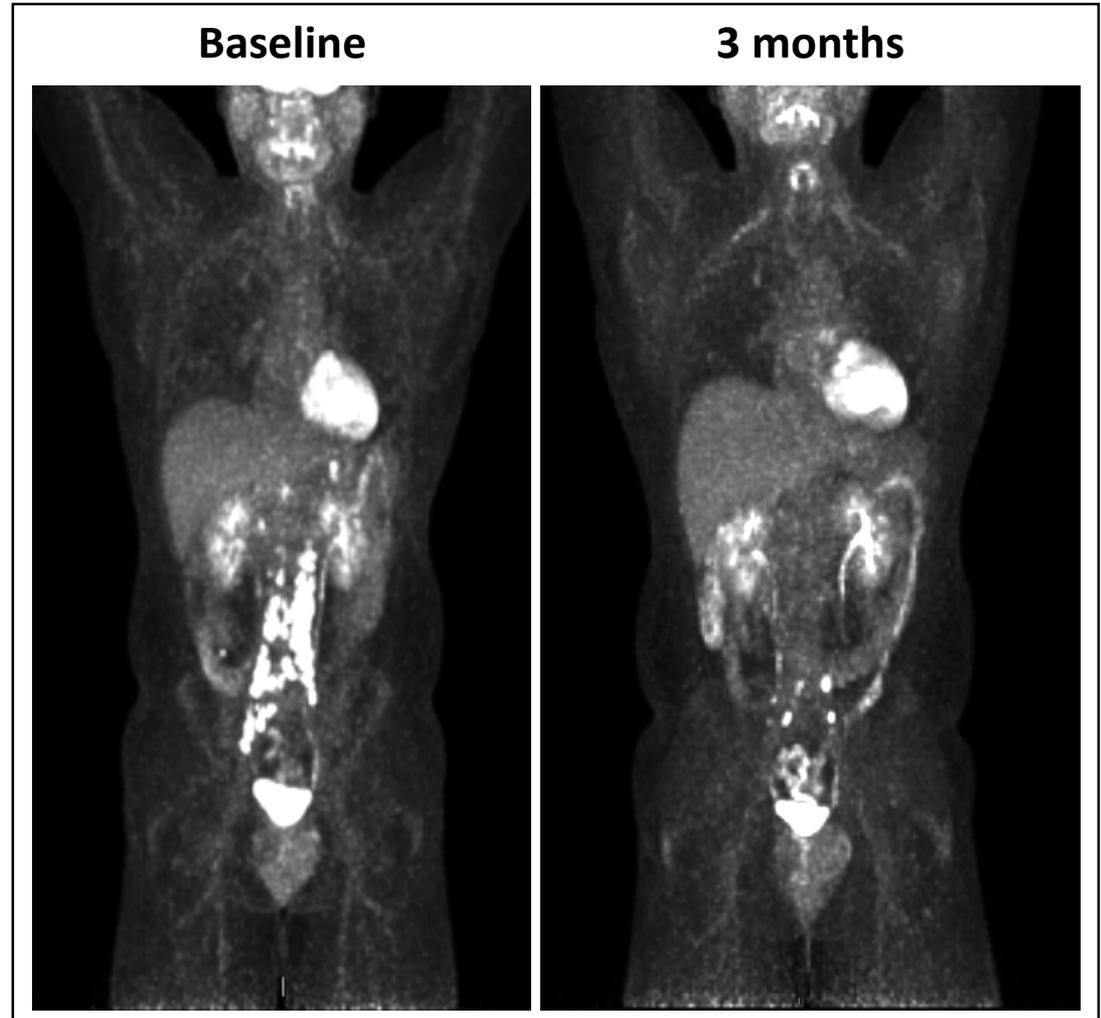


Patient 3



Patient 4

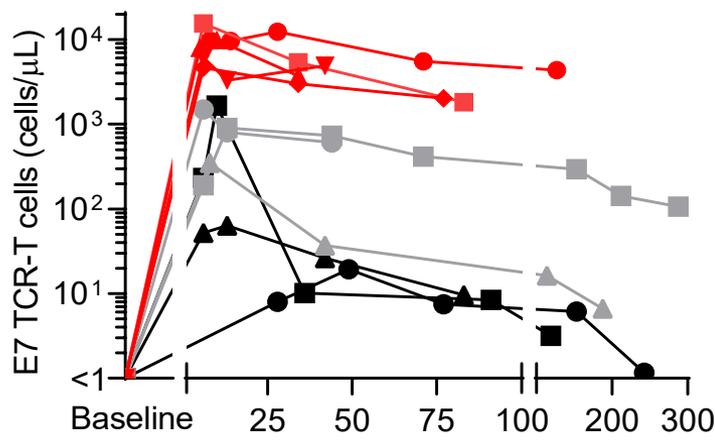
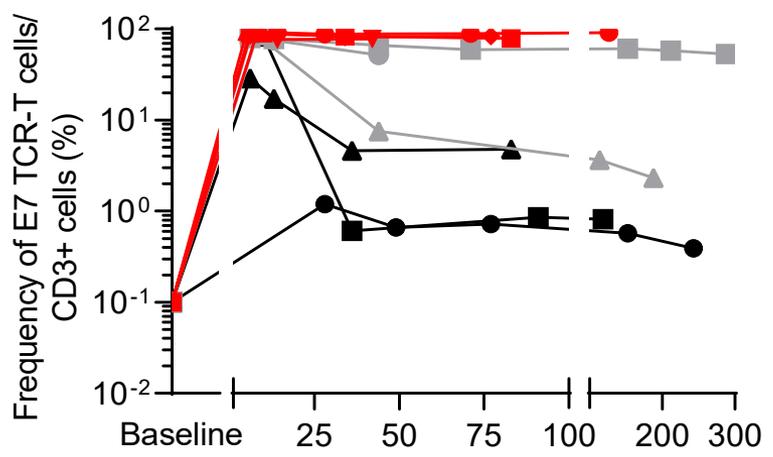
- 39-year-old male with esophageal cancer
- 6 prior systemic agents
- Prior pembrolizumab
- Multiple retroperitoneal metastases
- 7-month partial response



Summary of Phase I/II Data

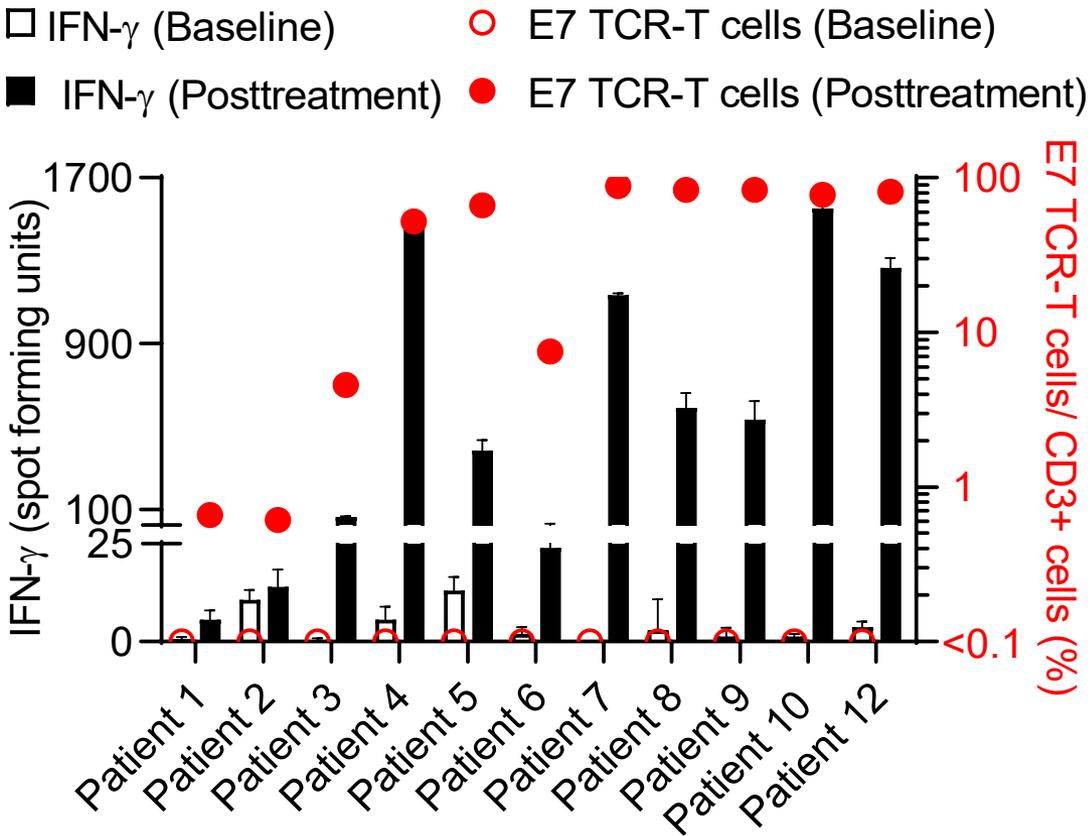
- **10/20 partial responses**
- **5/10 responses in PD-1-refractory disease**
- **Ongoing enrollment**

Persistence of E7 T cells in Blood

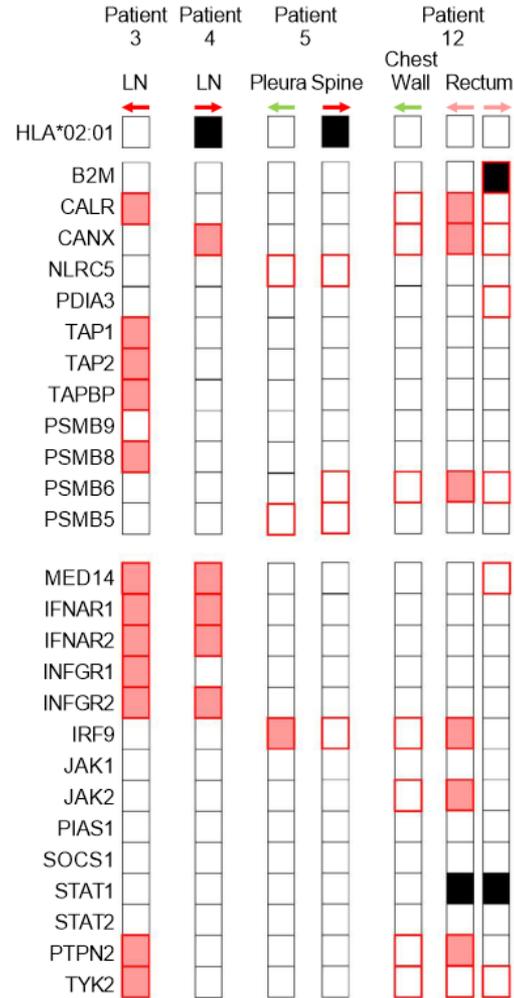
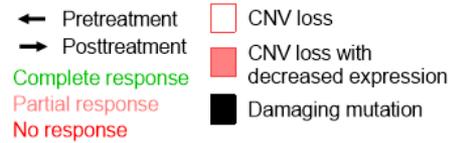


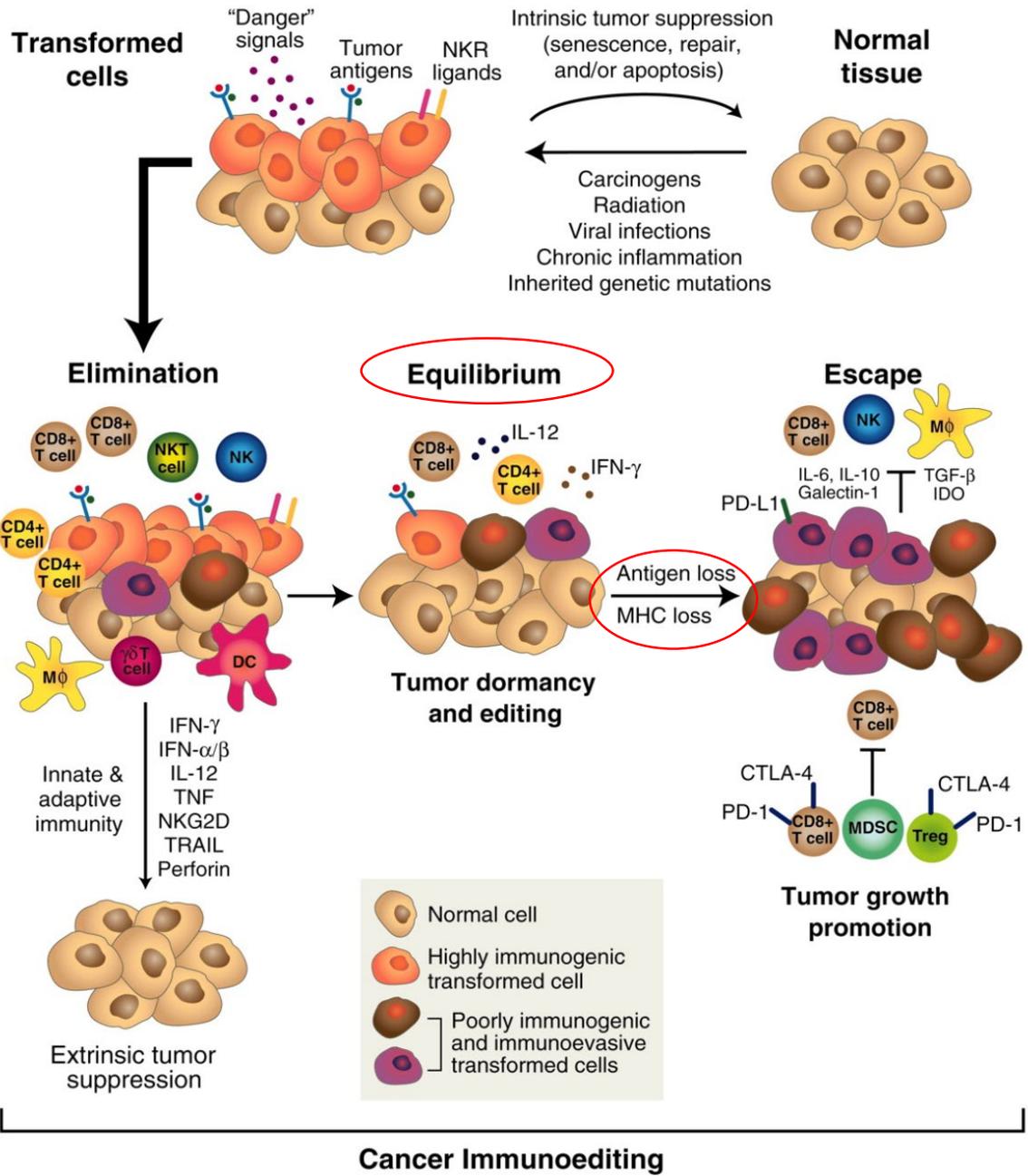
- DL1
- Patient 1
- Patient 2
- ▲ Patient 3
- DL2
- Patient 4
- Patient 5
- ▲ Patient 6
- DL3
- Patient 7
- Patient 8
- ▲ Patient 9
- ▼ Patient 10
- ◆ Patient 12

Function of Engrafted E7 T cells

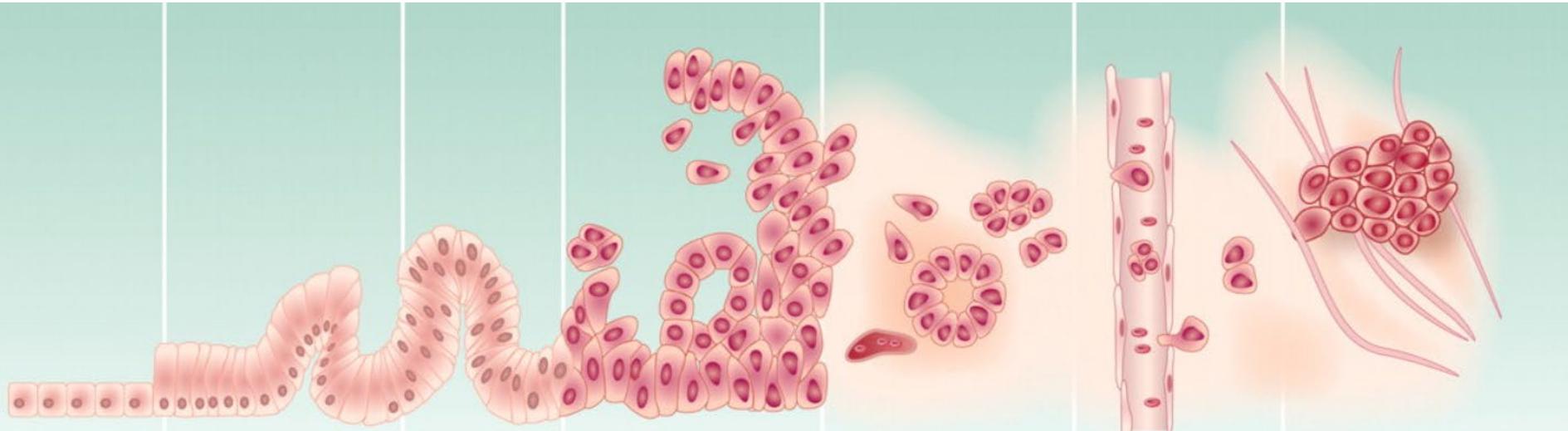


Tumor-Intrinsic Resistance to E7 T cells





Early Treatment with E7 TCR T cells



Healthy Tissue

Metastatic Cancer

- High grade CIN
- Vulvar HSIL
- Early Stage OPC
- Locally Advanced
 - OPC
 - Cervical
- E7 w/ tethered cytokines

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

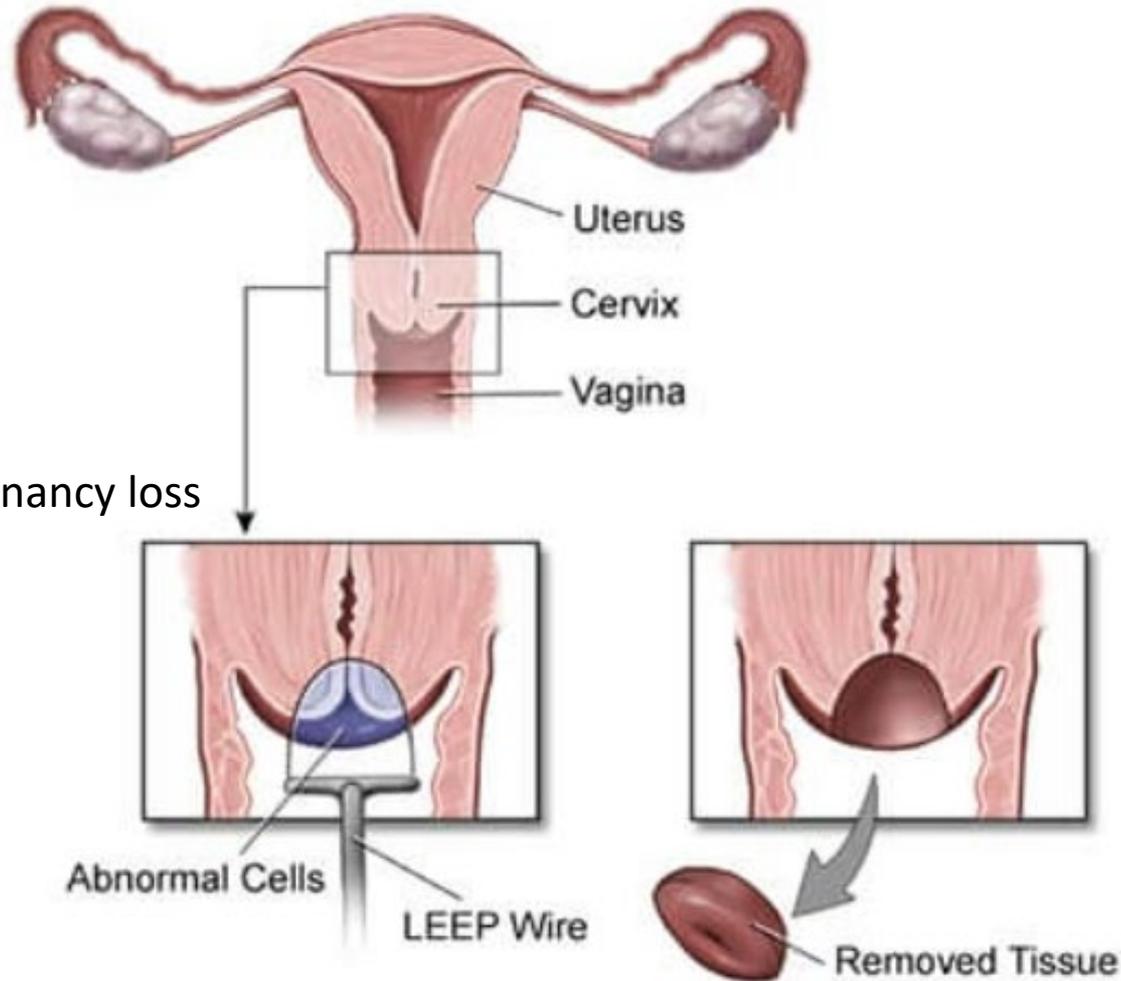
- **Phase II study**
- **Single IV infusion of 100 billion E7 TCR T-cells**
- **Eligibility**
 - **HPV-16+ vulvar HSIL, HLA-A*02:01**
 - **Measurable lesion(s) that are recurrent or cannot be resected w/o acceptable cosmetic or functional results**

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

Loop Electrosurgical Excision Procedure (LEEP)



Risks include:

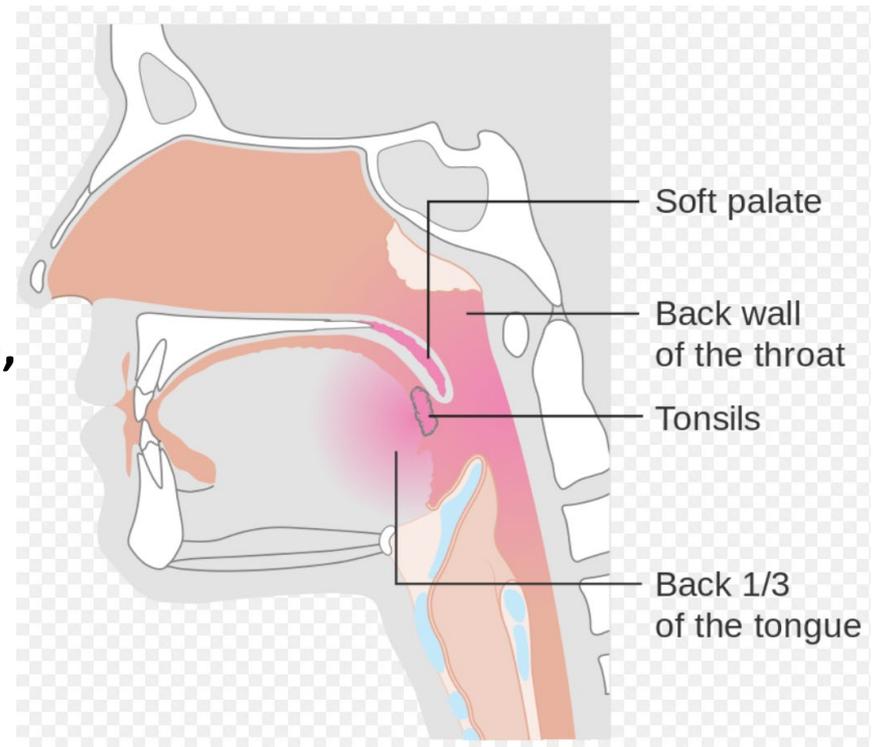
- Infertility
- PPROM
- Preterm delivery
- 2nd trimester pregnancy loss
- Perinatal death

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: 3×10^8 D0, 3×10^9 D31**
 - **DL2: 3×10^9 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



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

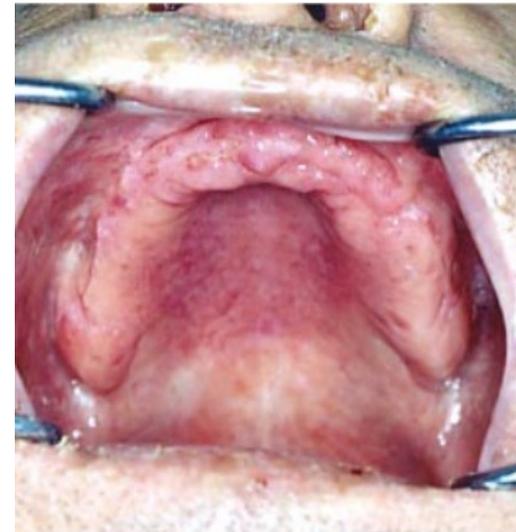
Mucositis



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

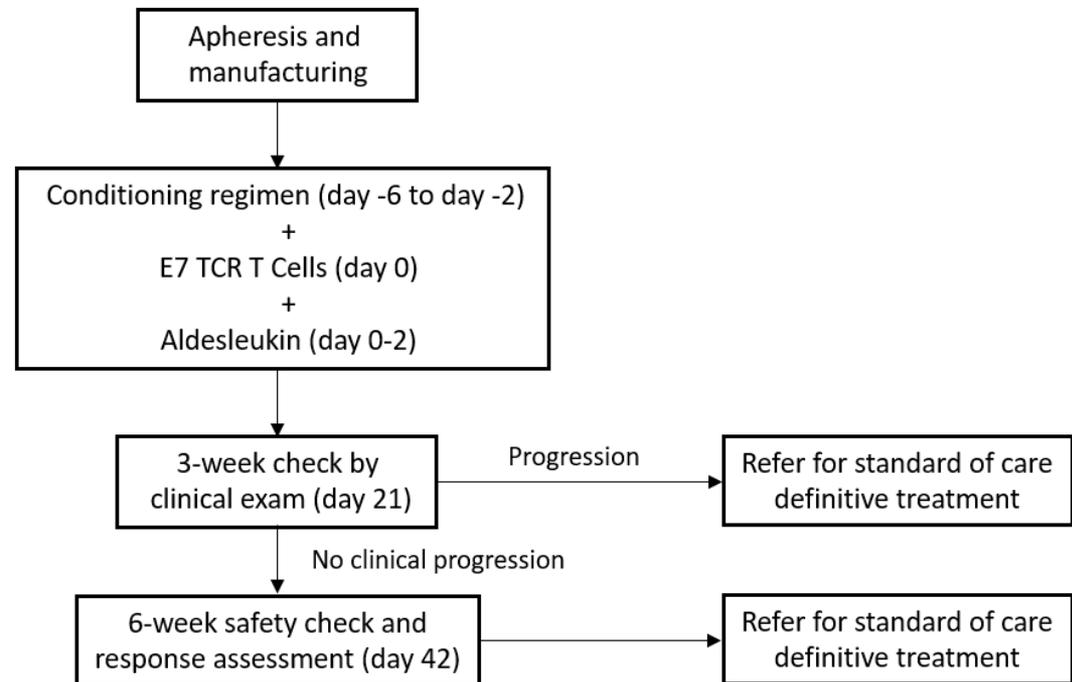
- **Borderline Resectable or Unresectable Stage I HPV16+ OPC**
- **Treatment-naïve, HLA-A*02:01**
- **No chemotherapy or aldesleukin**
 - **Local injection of E7 TCR T-cells into primary tumor and/or clinically palpable lymph node(s)**
- **Primary endpoint is feasibility**
 - **Referred to standard of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

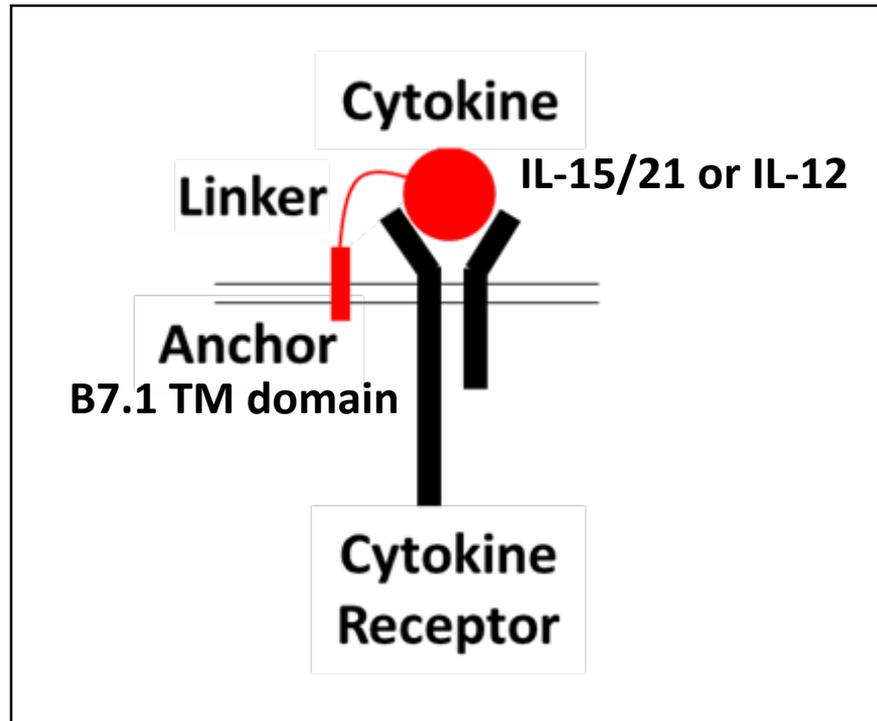
- **Feasibility study**
 - Toxicity delaying definitive tx
 - Increase in T and N stage
 - Chemo without getting cells
 - Dose reduction in chemoXRT
- **Lead-in safety cohort**
 - FIGO Stage IIIC-IVA
 - Stops if <3/5 patients are success



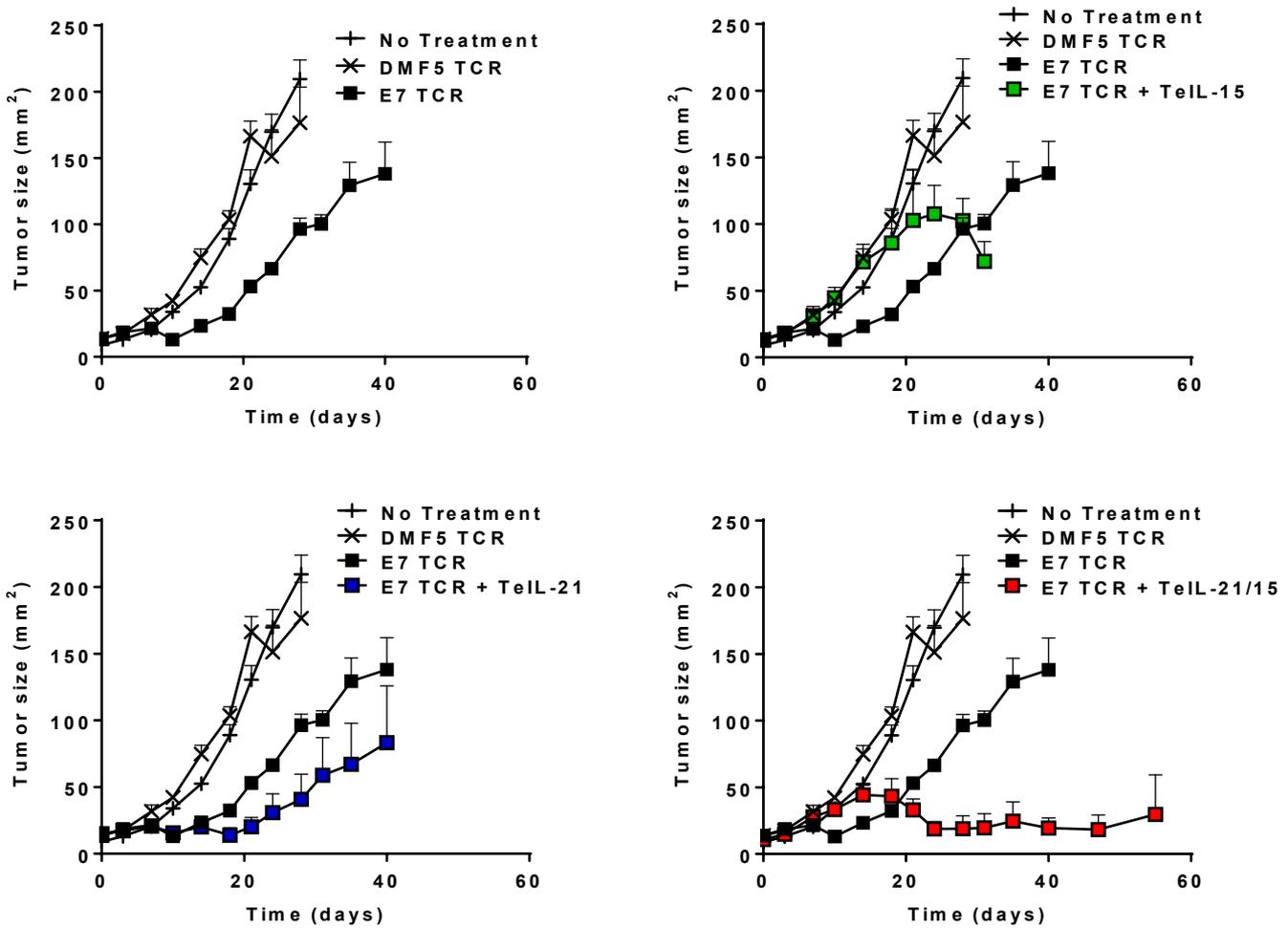
Clinical Program for HPV Disease

- **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



Membrane-Anchored IL-15/21



Expanding Cell Therapy Program

TARGET	DISEASE
Hepatitis B	Hepatocellular carcinoma
KK-LC-1	Epithelial cancer
EBV	EBV-associated malignancies
CD20	B-cell malignancies
CD22	B-cell malignancies
PAX5	B-cell malignancies

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**