Ciltacabtagene autoleucel (cilta-cel) immune effector cell enterocolitis is a clonal CAR+ lymphoproliferative disorder

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Background

Ciltacabtagene autoleucel (cilta-cel) is an autologous BCMA-targeting CAR-T currently approved in **2L+ setting in multiple myeloma.**

- **Unique structure with two camelid VHH chains**, allowing for camelid IHC staining.
- Cilta-cel can lead to durable response but can be associated with significant toxicity.

Immune effector cell-associated enterocolitis (IEC-EC) is an emerging toxicity that can develop after cilta-cel, often presenting with profuse, watery diarrhea, and abdominal pain.

- IEC-EC may develop from **post-CAR T-cell lymphoproliferation,** with some cases driven by **clonal CAR+ T-cell infiltration into GI tissues**.
- Cases can have **high morbidity and mortality** and are often **treatment-refractory.**
- The incidence, outcomes, and optimal management of IEC-EC remain poorly defined.

Objectives

- Describe incidence, clinical characteristics, treatment approaches and outcomes of all observed cases of IEC-EC at a single tertiary cancer center.
- Investigate the pathologic features of IEC-EC and evaluate clonality with anti-camelid immunohistochemical staining, flow cytometry, single cell RNA sequencing, whole exome sequencing, nested PCR sequencing, and whole genome sequencing.

Methods

- Single-center case series of IEC-EC cases
- Suspected IEC-EC identified by new enteritis/diarrhea prompting endoscopy with infectious evaluation per institutional standard of care.
- Compare cases of verified IEC-EC (with CAR T-cell infiltration, n = 9) to cases of post-cilta-cel enterocolitis not otherwise specified (EC-NOS, n = 8)
- All clinical details and treatments extracted from EHR.
- Biopsies reviewed with camelid (CAR) IHC. CAR+ IEC defined as >20% camelid+ infiltrates.
- COMET analysis used of camelid IHC by multiparametric fluorescent profiling and algorithmic counting of cells for camelid detection
- Clonality assessed in all cases by multiple methods.

Results

Table 1. Summary of clinicopathologic features and treatments among CAR+ IEC-EC cases (n=9)

Characteristic	Pt 1	Pt 2	Pt 3	Pt 4	Pt 24	Pt 32	Pt 52	Pt 67	Pt 147
Age/Sex	64 y/o F	67 y/o F	73 y/o M	67 y/o M	70 y/o F	65 y/o M	53 y/o F	63 y/o M	79 y/o F
Race/Ethnicity	African American	Hispanic	African American	Asian	Caucasian	African American	Hispanic	Caucasian	African American
ECOG PS	1	0	1	1	0	0	1	1	1
Myeloma Subtype	IgG Lambda	IgG Lambda	IgG Kappa	IgA Kappa	IgG Kappa	IgG Kappa	Kappa LC	IgG Kappa	IgG Lambda
R-ISS	II	II	III	III	II	I	I	II	II
Prior lines of therapy	5	4	4	4	6	5	4	6	3
Overall response	CR	CR	CR	CR	CR	CR	CR	PD	CR
IEC-EC directed treatments **Rx listed order of administration*	Dex IV Budesonide Mesalamine Vedolizumab Cytoxan Ruxolitinib	Cytoxan Dex IV Mesalamine	Cytoxan Dex IV Mesalamine Vedolizumab Ruxolitinib Budesonide Cyclosporine	Dex IV Ruxolitinib Carfilzomib	Budesonide Prednisone Beclomethasone	Budesonide Mesalamine Prednisone PO Solumedrol Methyl-prednisolone Infliximab Ustekinumab Dupilumab	Mesalamine	Dex PO and IV Anakinra Ruxolitinib Budesonide Mesalamine Cytoxan	Mesalamine Budesonide Cyclosporine Ruxolitinib Tacrolimus Vedolizumab

Table 2. Summary of complications and overall outcomes among CAR+ IEC-EC cases (n=9)

Characteristic	Pt 1	Pt 2	Pt 3	Pt 4	Pt 24	Pt 32	Pt 52	Pt 67	Pt 147
Symptom onset (relative to infusion)	D+37	D+64	D+61	D+30	D+541	D+66	D+47	D+75	D+56
CTCAE grade	3	5	4	5	—	5	3	4	4
Peak stool volume (mL/day)	10050 mL	2800 mL	13700 mL	—	—	—	—	1700 mL	—
Hospital LOS (days)	48 d	32 d	58 d	48 d	2 d	112 d	35 d	36 d	67+ d
ICU admission	No	No	No	Yes	Yes	Yes	No	Yes	No
TPN dependence	No	Yes (4 d)	Yes (37 d)	No	No	Yes (~330 d)	No	No	Yes (21 d)
Steroid exposure (mg pred equiv)	133 mg	227 mg	227 mg	280 mg	—	Unable to calculate	0 mg	1534 mg	—
Total # Infections	1	6	3	4	1	9	5	3	3
Overall outcome	Resolved (D+81)	Death (D+113)	Resolved (D+148)	Death (D+81)	Death (D+902)	Death (D+468)	Resolved (D+152)	Resolved (D+148)	Recurrent Symptoms

Figure 1. Greater TCR clonality of IEC-EC cases vs EC-NOS cases

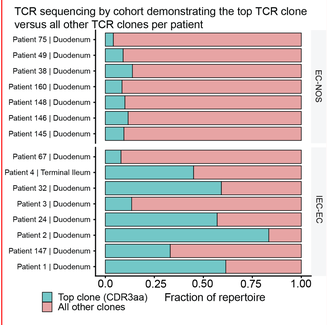


Figure 2. Clonal vector integration by nested PCR sequencing

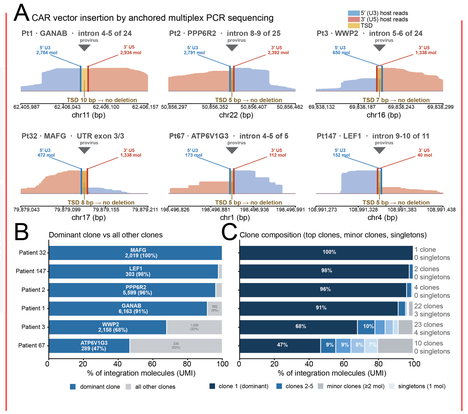


Figure 3. IEC-EC patients display greater CAR persistence after day 50

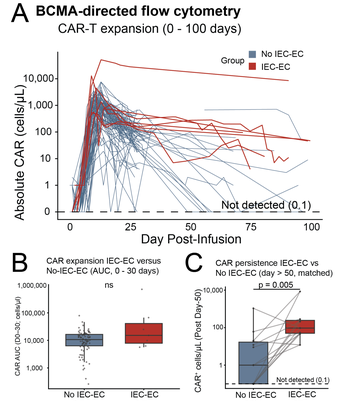


Table 3 Evidence for CAR clonality

Patient ID	Clinical TCR (PCR)	Clinical Flow	TCR-seq	WGS	scRNA	Nested PCR-seq
Patient_1	Oligoclonal TRG (colon, 8% infiltrate)	NA	Monoclonal	GNAB (58.3% of chimeric reads)	NA	GNAB (91% of reads)
Patient_2	Monoclonal TCRG, Monoclonal TCRB	Clonal CD4+ BCMA+ Population	Monoclonal	PPP6R2 (73.3% of chimeric reads)	Clonal CAR+	PPP6R2 (96% of reads)
Patient_3	Monoclonal TCRG, Monoclonal TCRB	Clonal CD4+ BCMA+ Population	Oligoclonal	WWP2 (50% of chimeric reads)	Clonal CAR+	WWP2 (68% of reads)
Patient_4	Monoclonal TCRG, Oligoclonal TRCB	NA	Monoclonal	CDK11B (40% of chimeric reads)	Clonal CAR+	NA
Patient_24	NA	NA	Monoclonal	CLIP3 (94.1% of chimeric reads)	NA	NA
Patient_32	NA	NA	Monoclonal	MAFG (55.5% of chimeric reads)	NA	MAFG (100% of reads)
Patient_52	Monoclonal TCRG	NA	NA	NA	NA	NA
Patient_67	Monoclonal TCRG (pre-treatment)	NA	Oligoclonal (post-treatment)	NA	NA	ATP6V1G3 (47% of reads)
Patient_147	Monoclonal TCRG, Monoclonal TCRB	Clonal CD4+ BCMA+ Population	NA	LEF1 (77.8% of chimeric reads)	NA	LEF1 (98% of reads)

Figure 4. Representative Immunofluorescent images of CAR+ T-cell infiltration

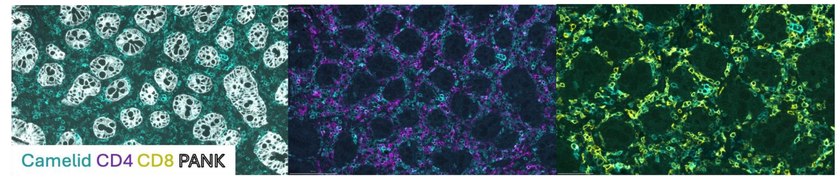
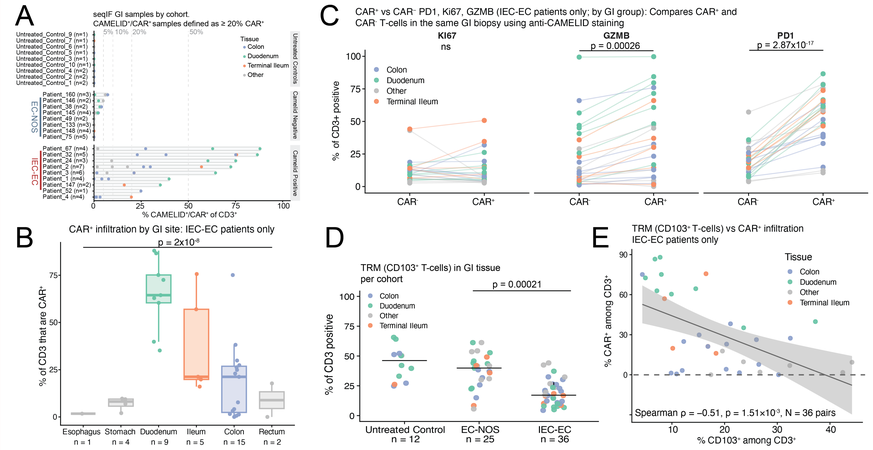


Figure 5. Characterization of CAR-positive cells by sequential immunofluorescence



Key Points:

- There were **9/154 cilta-cel recipients** and 0/70 ide-cel recipients with CAR+ IEC pathology
- **6-month cumulative incidence of IEC-E was 5.2%** (95% CI 1.7–8.7).
- **NRM 11.4% at 2 yrs**; ~40% NRM involved IEC-EC.
- **CAR+ IEC cases were high-grade** (CTCAE 3–5) with **onset typically ~ D+61** (range D+29–541).
- **Substantial morbidity and mortality** with med hospital LOS 48 d (range 2–112), ICU 4/9, TPN 4/9, and med 3 infections (range 1–9).
- All tested cases demonstrated **monoclonal or oligoclonal TCR populations**.

Conclusions

- **CAR+ IEC-EC after cilta-cel** occurs in a measurable minority of patients and is associated with **substantial morbidity** and contribution to NRM.
- Biopsies frequently show **dense CAR+ infiltrates** and **clonal/oligoclonal T-cell populations**, supporting a **CAR-driven lymphoproliferative process** that mimics indolent GI T-cell lymphoma.
- **Early endoscopy and biopsy with IHC and flow cytometry** to confirm infiltrate is crucial
- **T-cell directed approaches (e.g., cyclophosphamide)** may reduce CAR burden and symptoms, leading to durable remission. Careful balancing of infection risk and disease control should be considered.