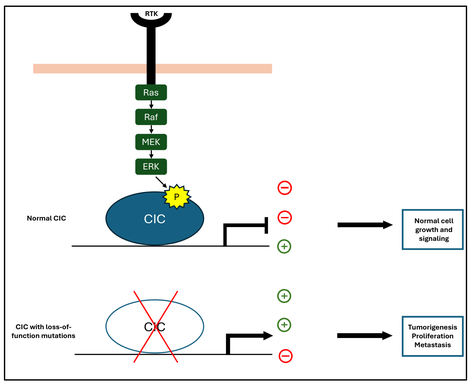
CAPICUA (CIC) MUTATIONS AS A NEGATIVE PROGNOSTIC MARKER IN ADULT T-CELL LEUKEMIA/LYMPHOMA (ATLL)

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Introduction

- Adult T-cell leukemia/lymphoma (ATLL) is a **rare, aggressive malignancy** of CD4+ T-cells caused by **HTLV-I infection**.
- The disease is **associated with poor outcomes**.
- **Chemotherapy and antiviral therapies** have shown **limited success**.
- **Allogeneic stem cell transplantation (SCT)** remains the **only curative option** for aggressive subtypes in remission.
- There are currently **no validated molecular markers** to predict treatment resistance or overall prognosis.



Objectives

1. **To risk-stratify** ATLL patients based on their molecular mutational profiles.
2. **To assess** whether a given mutational profile was associated with refractoriness to conventional therapies.

Methods

- Analyzed **37 patients** with **ATLL** from Montefiore Einstein Cancer Center
- Clinical, molecular, and pharmacologic **data** were available
- Targeted **next-generation sequencing of 236 genes** was performed
- Sequencing used **NeoGenomics** NextCourse Complete and Lymphoid Molecular Profile platforms
- Clinical data were abstracted from **electronic medical records**

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Results

- Our analysis identified **4 subjects** with the poorest prognosis who were refractory to conventional therapies.
- A **frameshift mutation** in the ***CIC* gene** was found to be present in all 4 of these cases (Table 1).
- These patients had significant complications during the course of their disease, including life-threatening **hypercalcemia** and **cytopenia**.
- Median overall survival (OS) for patients with the CIC mutation was **124 (47-350) days** compared to that of the rest of our cohort (n=33) of **834 days** (log-rank p-value = .00077) (Figure 2).
- The *CIC* gene in our cohort was associated with a **dismal prognosis** and was **refractory** to all therapies deployed.

	Case 1	Case 2	Case 3	Case 4
Age at diagnosis	82	48	32	61
Gender	F	F	F	F
Race	Black	Black	Black	Asian
OS (days)	47	168	350	80
Subtype	Leukemic	Leukemic	Leukemic	Lymphomatous
# of Regimens	0	4	5	3
Treatment at diagnosis	N/A	DA-EPOCH	CHOP	DA-EPOCH
Additional regimens	N/A	R-ICE PegIFN + Biktarvy Mogalizumab	Decitabine + ICE DA-EPOCH PegIFN CTX130 T-cells	ICE + Venetoclax Decitabine
Mutational profile	BRAF, CBL, CIC, EPOR, ERBB4, NOTCH1, STAT6	CARD11, CDKN2A, CIC, BTK, GNB1, NUP98, PLCG1, PTPRC, TNFAIP3	CIC, CUX1, ATG2B, BCOR, BRINP3, IRF4, TBL1XR1	ARID2, KLF2, TP53, ERBB2, FOXO1, CIC, EP300

Table 1: Profiles of the 4 patients from our cohort with the worst prognosis. They all have mutations in the *CIC* gene.

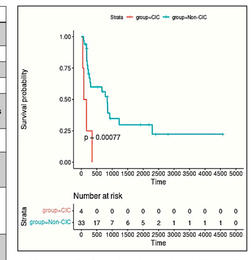


Figure 2: Survival probability of ATLL patients without a mutation in the *CIC* gene (n=33) versus survival of those with the *CIC* mutation (n=4).

Discussion

- Loss-of-function **CIC mutations** may be linked to particularly poor prognosis in ATLL
- This is the **first report** associating CIC mutations with poor outcomes in ATLL
- Findings suggest patients with CIC mutations should be prioritized for **clinical trials** and **early SCT**
- CIC likely acts via the **ERK/MAPK pathway**, promoting uncontrolled proliferation
- Further studies needed to clarify CIC's role in **T-cell regulation** and ATLL oncogenesis
- Results may not be universal due to **geographic differences** and other contributing mutations
- **Potential therapy:** Targeting ERK/MAPK pathway with **MEK/ERK inhibitors** in CIC-mutated ATLL

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