22nd International Conference on Human Retrovirology:
HTLV and Related Retroviruses
HTLV2026

June 3-6, 2026 | Philadelphia, Pennsylvania, USA

Symposium 7 - Therapeutic/ATLL

Chairs: Juan C. Ramos and Vidyasagar Koduri

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FIRST-IN-HUMAN CD70-DIRECTED ALLOGENEIC CAR T-CELL THERAPY FOR HTLV-1 ATLL: DURABLE RESPONSES AND MOLECULAR EVOLUTION IN THE COBALT-LYM TRIAL

Subset analysis from the First-in-Human COBALT-LYM Phase I Trial

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COBALT-LYM
Phase I Trial
NCT04502446

DISCLOSURE STATEMENT

PER Physician's Education Review (Faculty Advisor)	BioHeng
Morphosys Advisory Board	Bristol Myers Squibb Foundation Diversity in Clinical Trials Program Scholar Award
Miragen	Curio
Kite Pharma (MTA Agreement and Research Funding)	NIH K12 Calabresi training award
CRISPR Therapeutics	

OVERVIEW

01

ATLL:
The Challenge

02

CTX130:
The Therapy

03

COBALT-LYM:
Trial Design

04

Results &
Genomic Insights

Key Question:

Can CRISPR-engineered, allogeneic, off-the-shelf CAR T cells targeting CD70 provide safe and effective therapy for relapsed/refractory Adult T-Cell Leukemia/Lymphoma (ATLL) — a rare, aggressive malignancy with no established salvage options?

ATLL: AN AGGRESSIVE MALIGNANCY WITH CRITICAL UNMET NEED

Disease Overview

- Aggressive CD4+ T-cell malignancy associated with HTLV-1
- ~10-20 million people infected worldwide; 2-5% lifetime risk of ATLL
- Caribbean, sub-Saharan Africa, Southwest Japan endemic regions
- Predominates in underserved minority populations in Bronx/NYC
- Subtypes: acute, lymphomatous, chronic, smoldering (Shimoyama)
- Immunophenotype: CD4+/CD8−/CD7−/CD25+, ~50% FoxP3+
- Median OS: 6-7 months (US, aggressive subtypes)
- Worst OS among all peripheral T-cell lymphomas (SEER data)

6-7 mo

Median OS
(US aggressive)

~92%

Aggressive subtype
(N. American)

~30%

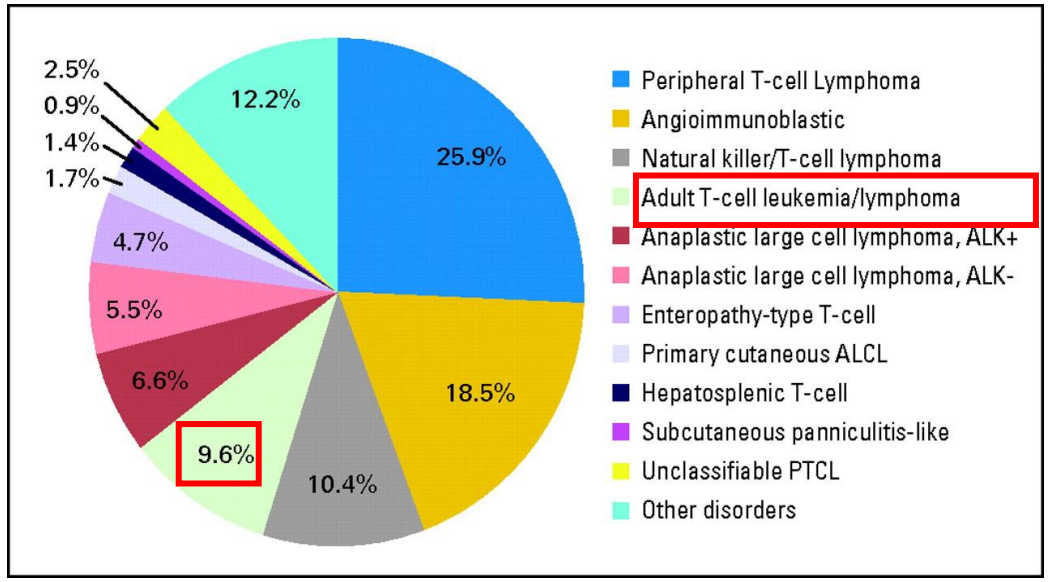
CNS involvement
(US patients)

12.3%

Transplant access
in our cohort

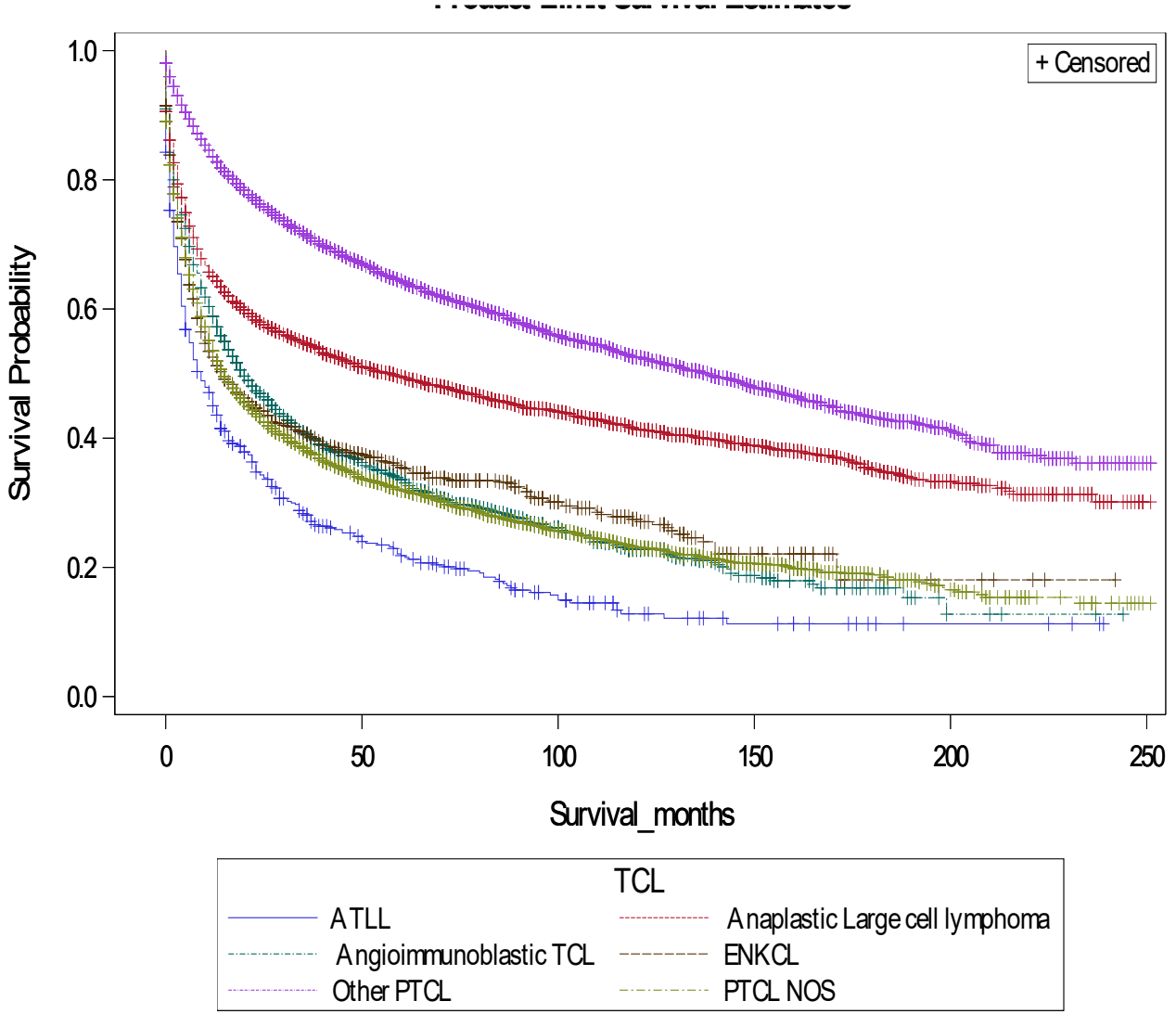
ATLL HAS THE WORST OS AMONG ALL PTCLs

The International T-Cell Lymphoma Project JCO 2008



- **1,314 cases between 1990 and 2002**
- **Worldwide: 9.6% of PTCL**
- **US: 2%-3% of PTCL**
- **Japan: 25% of PTCL**

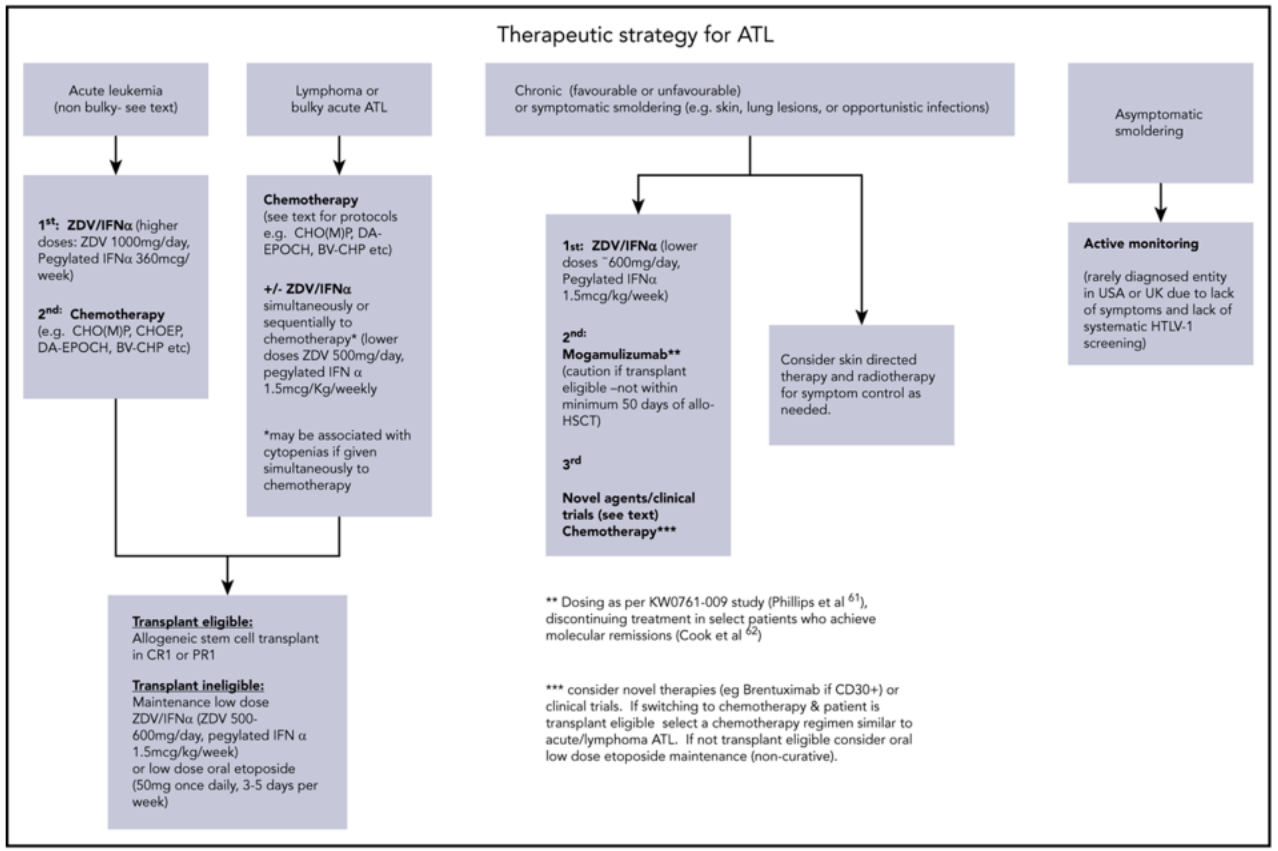
US SEER T-Cell Lymphoma Survival Estimates



ATLL: TREATMENT RECOMMENDATIONS (COOK ET AL.)

Adult T-Cell Leukemia/Lymphoma (ATLL)

Treatment recommendations (Cook et al):



Lucy B. Cook,Adrienne A. Phillips, How I treat adult T-cell leukemia/lymphoma, Blood, 2021,

TREATMENT LANDSCAPE AND THE RATIONALE FOR ALLOGENEIC CAR T

Chemotherapy (EPOCH-based) → Mogamulizumab → AlloSCT (only curative) → Relapse / No Donor Access → **NO ESTABLISHED SALVAGE THERAPY**

Why NOT Autologous CAR T in ATLL?

- ✕ Patient T cells are malignant — contamination risk
- ✕ Poor T-cell function in HTLV-1 infected cells
- ✕ Fratricide: CAR T cells destroy each other
- ✕ Time to manufacture not feasible in aggressive disease
- ✕ T-cell aplasia and profound infection risk

Why Allogeneic (Off-the-Shelf) CAR T?

- ✓ Healthy donor T cells — no tumor contamination
- ✓ Immediate availability — critical for aggressive ATLL
- ✓ CRISPR edits prevent GvHD and immune rejection
- ✓ Scalable manufacturing for rare/underserved populations
- ✓ Enables re-dosing (multiple infusions permitted)

CTX130: CD70-DIRECTED ALLOGENEIC CRISPR-Cas9 CAR T CELL

Why Target CD70?

- CD70 is a ligand for CD27 — transient expression on activated normal lymphocytes
- 85% of T-cell lymphoma samples express CD70 (median 40% surface expression)
- Aberrantly overexpressed in ATLL — immune evasion target
- ATLL CD70 expression drives T-cell exhaustion, apoptosis, Treg expansion
- Limited expression on normal tissues = favorable safety window
- Knockout of CD70 on CAR T product prevents fratricide / self-targeting

CRISPR-Cas9 Engineering of CTX130

① **TRAC KO**
Prevents GvHD (TCR disruption)

② **β2M KO**
Avoids host immune rejection

③ **CD70 KO**
Prevents fratricide (self-targeting)

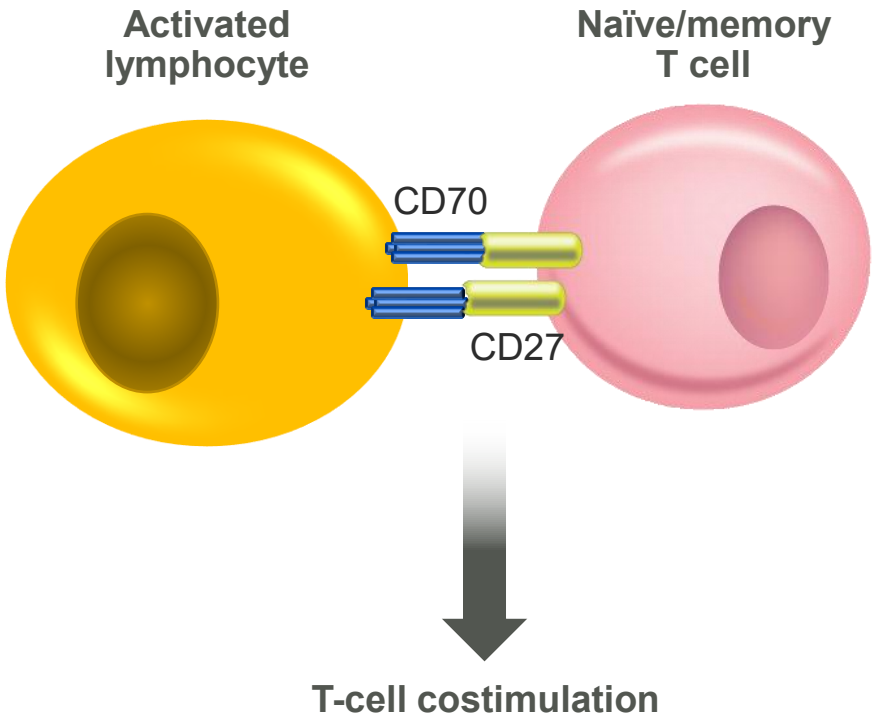
④ **Anti-CD70 CAR Insert**
Inserted into TRAC locus via homology-directed repair

Healthy Donor T Cells → CRISPR Edit → Expansion → Cryopreservation → Off-the-Shelf Infusion

Role of CD70 in Immune Response and Cancer

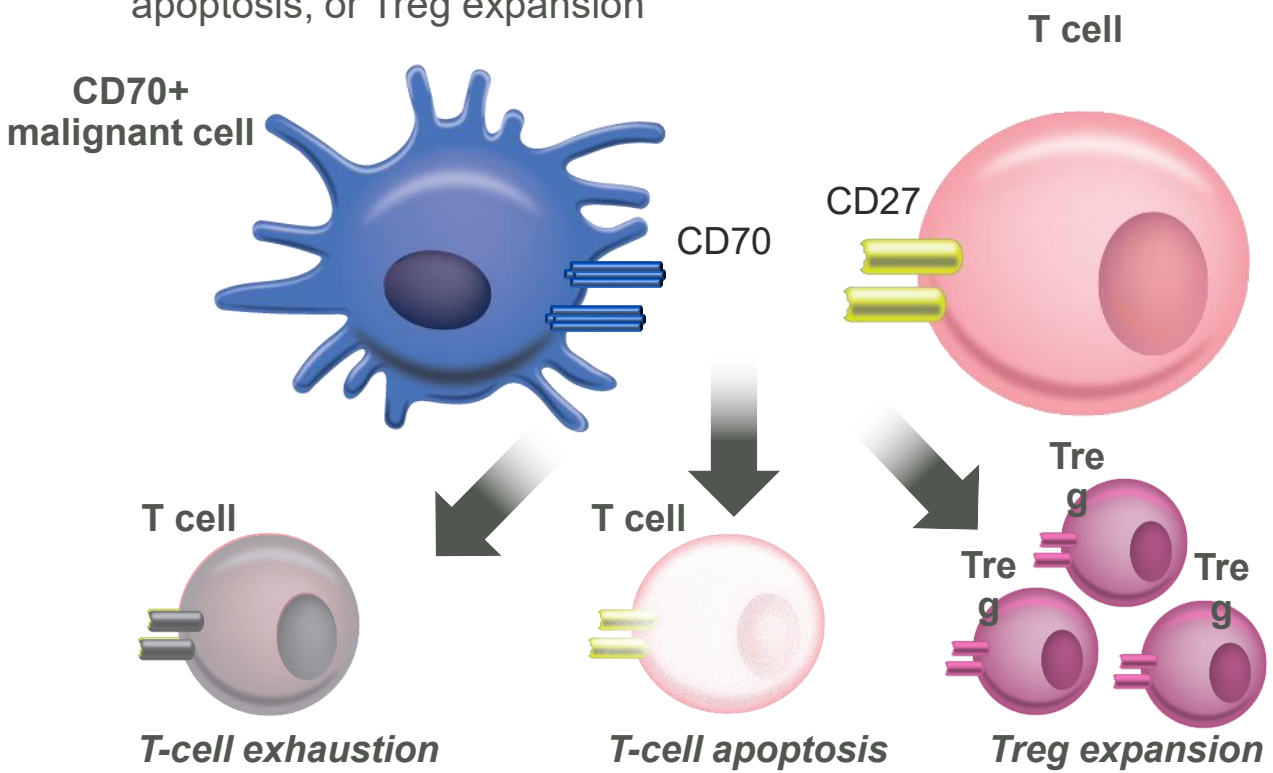
Physiological role of CD70[1]

- Transient CD70 expression on activated lymphocytes
- Controls naïve and memory T-cell activation via interaction with CD27



Role of CD70 in cancer[1]

- Increased CD70 expression has been **detected in certain cancers, including 85% of TCL samples** with a median surface expression of 40%[2]
- Possible immunosuppressive role due to T-cell exhaustion, apoptosis, or Treg expansion



TCL, T cell lymphoma; Treg, regulatory T cell.

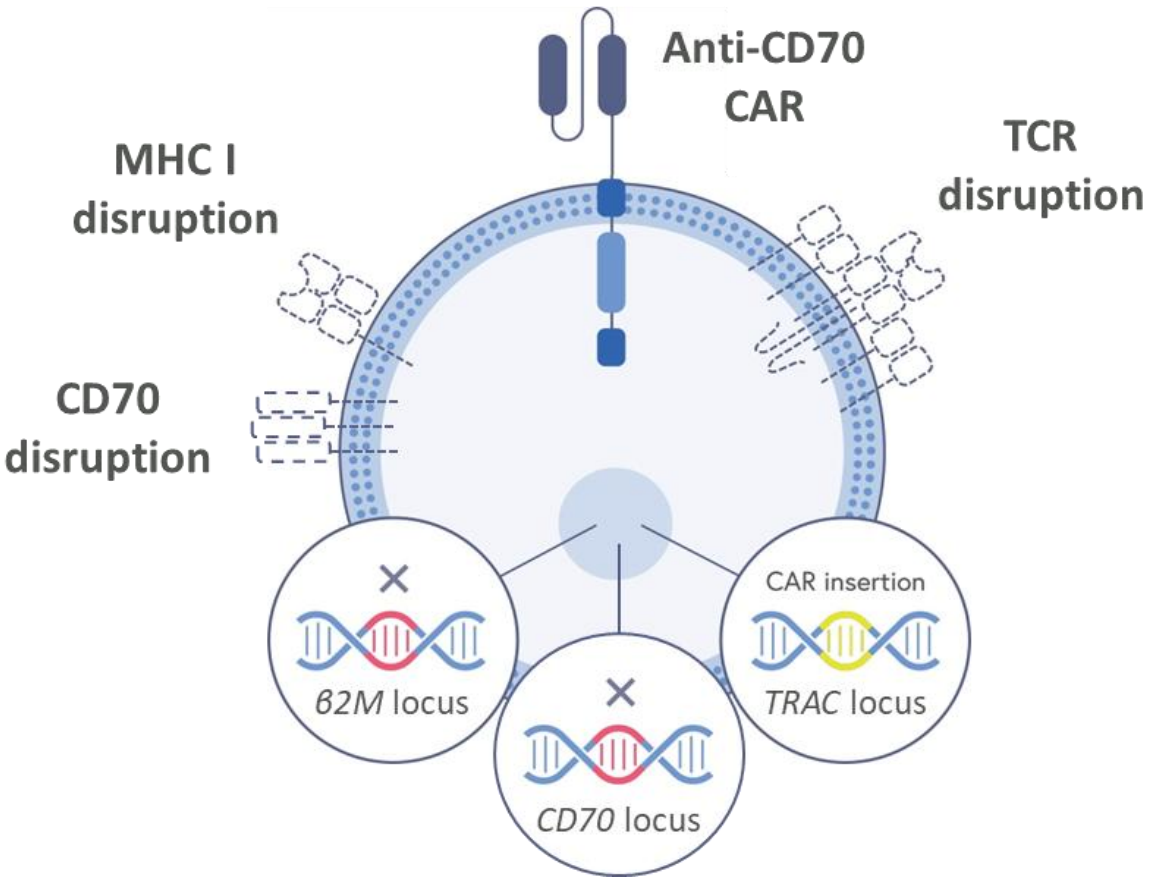
References: 1. Wajant H. *Expert Opin Ther Targets*. 2016;20:959-973. 2. Marques-Piubelli M, et al. *Histopathology*. 2022 Apr 26. doi: 10.1111/his.14670. Online ahead of print.

Presented at the European Hematology Association Annual Meeting. 11 June 2022

CTX130

- **Autologous approaches continue to be challenging** due to the poor function of donor T cells, potential for fratricide, and risk of infusing transduced malignant CAR T cells into patients
- **CTX130 is an investigational allogeneic, CRISPR/Cas9 gene-edited, anti-CD70 CAR T cell therapy** with TRAC, β2M, and CD70 disruptions
  - An **anti-CD70 CAR cassette is site-specifically inserted into the TRAC locus** by homology-directed repair
- **CTX130 is manufactured from T cells collected from a healthy donor,** which are then selected and edited before expansion and cryopreservation for **off-the-shelf availability**

CTX130 Construct

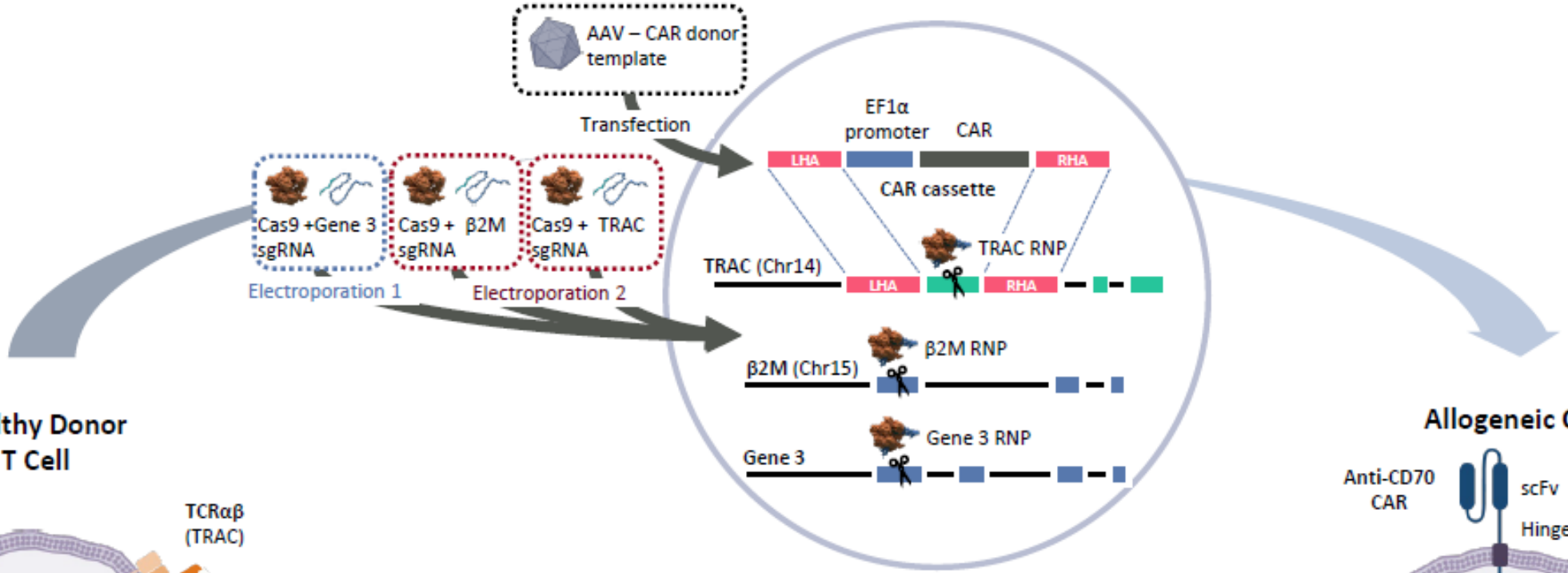


β2M, β2-microglobulin; CAR, chimeric antigen receptor; MHC, major histocompatibility complex; TCR, T-cell receptor; TRAC, T-cell receptor alpha constant.

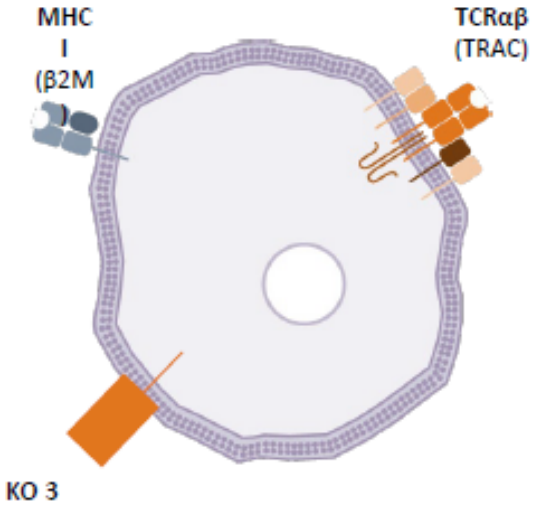
Reference: Dequeant M-L, et al. CD70 knockout: A novel approach to augment CAR-T cell function. Poster presented at American Association for Cancer Research 2021. April 10-15 and May 17-21, 2021.

Presented at the European Hematology Association Annual Meeting. 11 June 2022

Two-Step Multiplex Editing to Produce Allogeneic CTX130

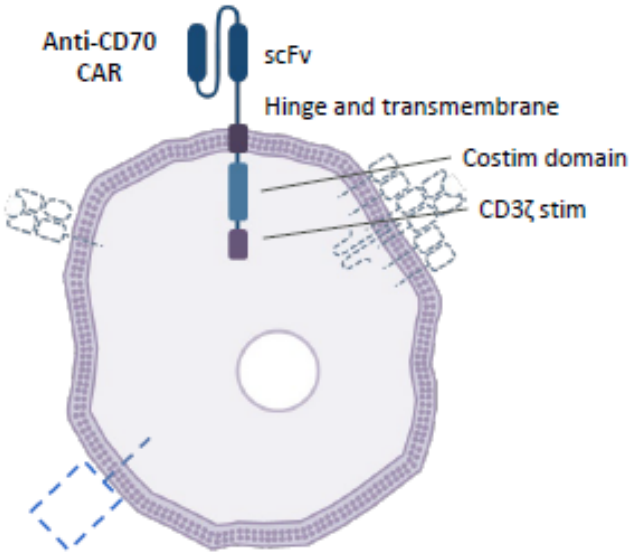


Healthy Donor T Cell



- **To prevent GvHD,** TCR expression is disrupted using CRISPR/Cas9 targeted to the TRAC locus
- **The anti-CD70 CAR construct** is inserted into the TRAC locus by homology-directed repair using an AAV template
- **To enhance persistence of allogeneic cells,** MHC-I expression is eliminated by disrupting the β2M gene
- **To improve T cell function,** Gene 3 expression is disrupted

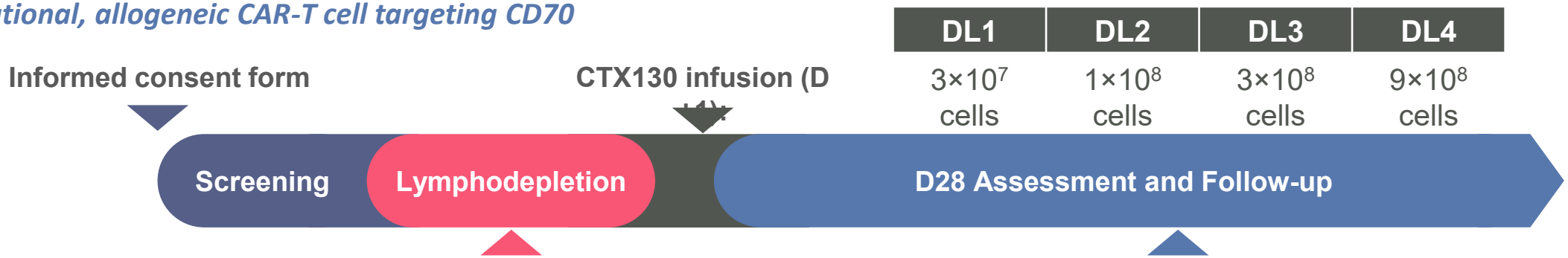
Allogeneic CTX130



Slide courtesy of CRISPR Therapeutics

COBALT-LYM (NCT04502446) Clinical Trial Design

Phase 1, open-label, multicenter, international, single-arm study (NCT04502446) evaluating the safety and efficacy of CTX130, an investigational, allogeneic CAR-T cell targeting CD70



Key inclusion criteria

- Age ≥18 years
- Confirmed diagnosis of a **CD70+ (≥10% of cells)** T-cell malignancy
- ECOG performance status of 0−1
- Adequate renal, liver, cardiac, and pulmonary organ function
- **Platelets >25,000/mm³** and **absolute neutrophil count >500/mm³**

Key exclusion criteria

- Prior allogeneic SCT
- Prior treatment with any anti-CD70 agents
- History of certain CNS, cardiac, or pulmonary conditions

Primary endpoint

- Part A (Dose Escalation): Incidence of adverse events
- Part B (Cohort Expansion): Objective response rate*

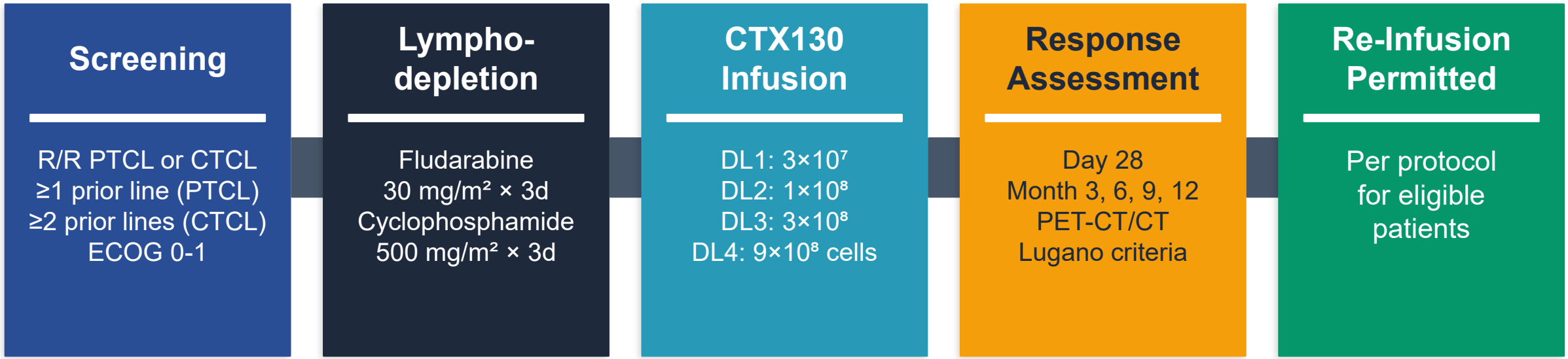
Secondary endpoints

- Progression-free survival
- Overall survival

*As assessed by Lugano response criteria for PTCL, International Society for Cutaneous Lymphoma Response Criteria for CTCL.
CNS, central nervous system; CR, complete response; CTCL, cutaneous T cell lymphoma; D: day; LD, lymphodepletion; PD, progressive disease; PR, partial response; PTCL, peripheral, T cell lymphoma; SCT, stem cell transplant; SD, stable disease.

Presented at the European Hematology Association Annual Meeting. 11 June 2022

COBALT-LYM: PHASE 1 TRIAL DESIGN



Study Enrollment

- 10 medical centers: USA, Australia, Canada
- Aug 2020 – May 2023: 41 patients enrolled
- 39 patients (95%) received CTX130
- **9** ATLL patients (7 at Montefiore Einstein, Bronx)
- Median follow-up: 7.4 months (IQR 3.1–12.2)

Endpoints

Primary: Dose-limiting toxicities (DLT) within 28 days

Secondary: Overall response rate (ORR), PFS, OS

Exploratory: CTX130 expansion/persistence in blood

Sica Lab: NGS mutational profiling (NeoGenomics)

Sica Lab: Long-term follow-up through July 2025

PATIENT DEMOGRAPHICS: FULL COHORT & ATLL SUBGROUP

Overall COBALT-LYM Cohort (N=39)

Characteristic	Value
Female / Male	54% / 46%
Race: White / Black / Asian	62% / 21% / 8%
PTCL / CTCL	56% / 44%
Stage IV	76.5%
Median prior therapy (PTCL)	2.5 lines (IQR 1.3–4.0)
Median prior therapy (CTCL)	5.0 lines (IQR 5.0–7.0)
Re-infusion rate	41%
DL4 (9×10^8 cells)	67%

ATLL Subgroup — Montefiore Cohort (N=6*)

Characteristic	Value
Median age at infusion	54 years (33–72)
Median prior therapy	1 line (range 1–5)
Acute/leukemic subtype	2 patients (29%)
Lymphomatous subtype	5 patients (71%)
Enrollment period	Aug 2020 – May 2023
Long-term follow-up	Through July 2025
Survivors as of July 2025	2 of 6 (longest: 37.5 mo)
Bridged to AlloSCT	1 patient

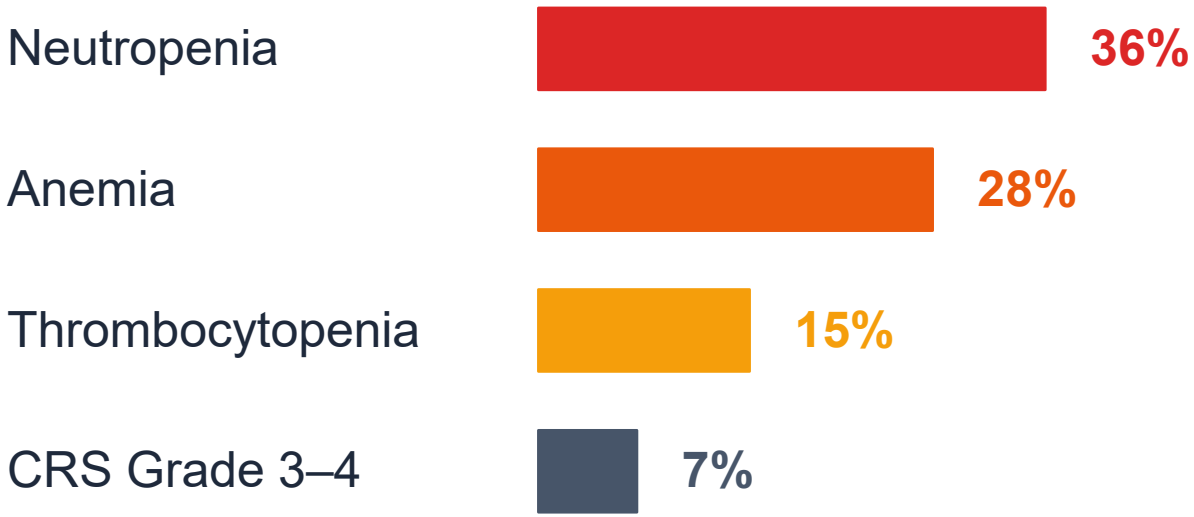
SAFETY PROFILE: MANAGEABLE ADVERSE EVENTS

67%
Cytokine Release Syndrome (any grade)

10%
ICANS (all Grade 1–2)

0 GvHD
No graft-vs-host disease (TRAC/β2M knockouts effective)

Most Common Grade 3–4 Adverse Events (N=39)



CRS Breakdown

Grade 1–2: 23 patients (59%)

Grade 3: 2 patients (5%)

Grade 4 (DLT at DL4): 1 patient (3%)

5 AE-related deaths: None CTX130-related

EFFICACY: OVERALL COHORT & ATLL SUBGROUP OUTCOMES

46.2%

ORR (overall, N=39)

95% CI: 30.1–62.8%

51.6%

ORR at DL3+ (DL≥3×10⁸)

Higher dose = better response

19.4%

Complete Response (DL3+)

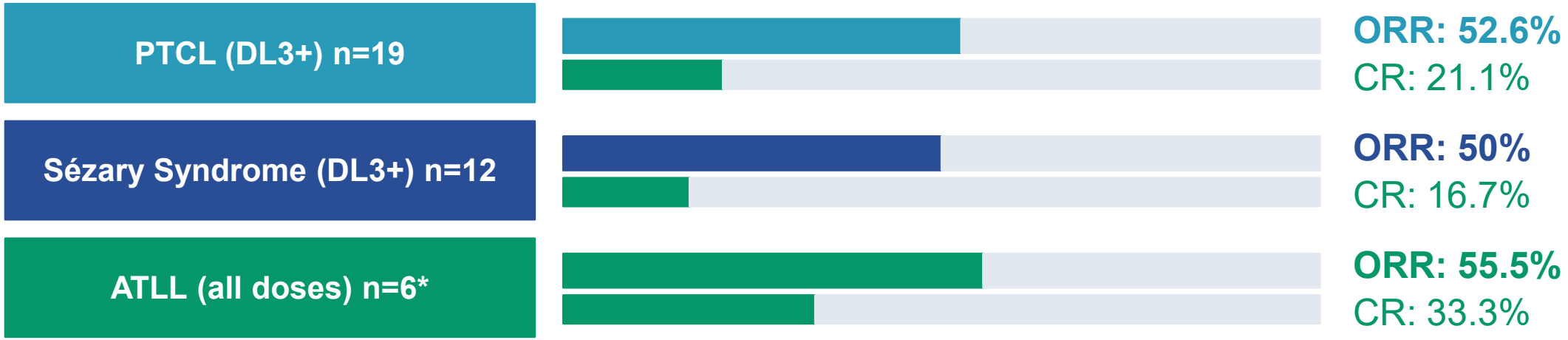
Including ATLL patients

NR

Median DOR (Sézary, DL3+)

Duration of response not reached

Response by Disease Subtype at DL3+ (preferred dose range)



** Montefiore cohort; ATLL data from Cordover et al., Blood 2025 (Supplement). ORR includes all responses; CR=complete response.*

ATLL COHORT: PATIENT CHARACTERISTICS AND OUTCOMES

Patient#	Subtype	Treatments	Adverse Effects to CTX130/LD	Best Response	PFS	OS	Additional treatments after CTX130	Cause of Death	Mutation profile
1. 40 y/o M	Lymphomatous	EPOCH X4 Radiation Therapy	None (received lowest dose DL1)	CR	87 days	2 Yr 2 months	Decitabine-DHAP Mogamulizumab ICE+Venetoclax CD5 CART cells Radiation therapy T-Vec ESHAP	ATLL Progression	ZFHX4 (P3546L) ZFHX4 (V487L) ⇩ ZFHX4 (P3546L) ZFHX4 (V487L) EP300 (G152S)
2. 69 y/o F	Lymphomatous	CHOP ICE BEAM IFN/AZT Pralatrexate	None	PD	N/A	7 months	HyperCVAD-Decitabine	ATLL Progression	N/A
3.33 y/o F	Acute/leukemic	CHOP	CRS G1 ICANS G1 HHV-6 Encephalitis	SD	N/A	76 days	None	HHV-6 Encephalitis	CIC (F1052F) CUX1 (Q1032)
4 . 60 y/o M	Lymphomatous	EPOCH Decitabine-Venetoclax	None	PD	N/A	75 days	ESHAP	ATLL progression	N/A
5. 40 y/o M	Lymphomatous	CHOEP ICE	None	PR	61 days	Not reached (+ 3 years)	EPOCHX3 Venetoclax Biktarvy Allogeneic SCT	Alive	N.A
6. 68 y/o F	Acute/leukemic	EPOCH IFZ/AZT	None	CR	6 months	Not reached (+ 3.5 years)	Moga PEG/IFN Biktarvy	Alive	*See next Acquires STAT3

ATLL CASE HIGHLIGHTS: RESPONSES IN RELAPSED/REFRACTORY DISEASE

Case 1: CR after Re-Infusion

Patient: 54-year-old lady, Stage IV ATLL with skin involvement

Prior therapy: 2 lines (IFNα-b + zidovudine, then relapse)

CD70 expression: 100% skin, 1% lymph nodes

1st infusion (DL3): PR at Day 28 → SD at Month 3

2nd infusion (DL4): CR at Day 28 — skin mSWAT: 3.6 → 0

Bone marrow: 25% ATLL → 1.3% aberrant cells post-tx

Outcome: Bridged to allogeneic stem cell transplant

✓ Complete response + AlloSCT bridge — ongoing survival

Case 2: Genomic Plasticity & Long-Term Survival

Patient: 67-year old lady with acute ATLL, multiple relapses after 2 lines of treatment (EPOCH and IFNα-b + zidovudine)

CTX130 therapy: Received DL3

Response: Achieved partial response, extended disease control

Key finding: Post-treatment STAT3 mutation acquired

STAT3 significance: Previously associated with more indolent ATLL phenotype

NGS data: Dynamic shifts in clonal architecture post-CTX130

Long-term OS: 37.5 months (longest survivor in cohort)

★ STAT3 acquisition → possible immune escape & disease attenuation

GENOMIC EVALUATION: NGS FINDINGS IN ATLL SUBGROUP

Genomics Methods & Cohort

Platform: Next-Generation Sequencing (NGS) via NeoGenomics

Patients: 3 of 6 ATLL patients had mutational profiling

Timepoints: Pre-CTX130 and post-CTX130 paired samples available in 2 patients

Analysis: Variant allele frequency (VAF) tracking across treatment

Focus: Clonal evolution, resistance mechanisms, prognostic mutations

Context: First genomic characterization of ATLL response to CAR T therapy

Key Genomic Findings

Clonal Plasticity Under CAR T Pressure

Dynamic VAF shifts observed in multiple genes — ATLL exhibits clonal adaptation during sustained immunological pressure from CTX130

STAT3 Mutation Acquisition

One long-term survivor developed post-treatment STAT3 mutation — previously linked to favorable, indolent ATLL phenotypes → possible immune-editing to less aggressive clone

New Mutation Emergence

Novel mutations acquired after CTX130 suggests ongoing genomic evolution, potentially limiting aggressive phenotype

Implications for Treatment Strategy

Genomic monitoring post-CAR T may identify patients with favorable clonal evolution; CAR T → AlloSCT consolidation critical before resistance emerges

GENOMIC EVALUATION: NGS RESULTS — CASE 6 (LONG-TERM SURVIVOR)

1/12/2022

Profile Results Detail

Molecular Testing Detail

Variants of Unknown Clinical Significance	Variant Allele Frequency (%)
EPOR V459I NM_000121.4:c.1375G>A	47.2
ESR1 I326V NM_001122742.1:c.976A>G	50.3
JAK2 D869G NM_004972.3:c.2606A>G	34.7
PDGFRB V523M NM_002609.4:c.1567G>A	46.6
TBL1XR1 S188Y NM_024665.6:c.563C>A	32.5

9/15/2023

Profile Results Detail

Molecular Testing Detail

Genes (SNVs/ Indels)	Amino Acid Change	Nucleotide Change	Consequence	Classification	Variant Allele Frequency (%)	Read Depth
ARID2	p.I378fs*29	NM_152641.4: c.1084dup	Frameshift	Pathogenic	51.2	1301
STAT3	p.P715L	NM_139276.2: c.2144C>T	Missense,Splice region	Pathogenic	16.2	1030

Variants of Unknown Clinical Significance	Consequence	Variant Allele Frequency (%)
EBF1 R209W NM_001290360.3:c.625C>T	Missense	16.0
EPOR V459I NM_000121.4:c.1375G>A	Missense	36.7
FANCI C1167G NM_001113378.1:c.3499T>G	Missense	47.0
IL7R I3L NM_002185.5:c.7A>C	Missense	11.4
JAK2 D869G NM_004972.3:c.2606A>G	Missense	11.6
PDGFRB V523M NM_002609.4:c.1567G>A	Missense	30.6
TBL1XR1 S188Y NM_024665.6:c.563C>A	Missense,Splice region	15.8
IKZF2::AC079610.1	Fusion	N/A

CTX130 CAR-T Therapy

Clonal Evolution in T-Cell Malignancy

Before CTX130
(1/12/2022)

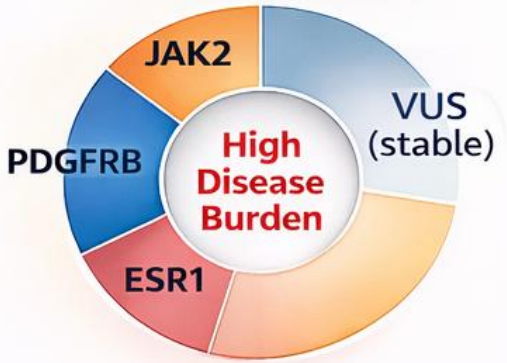
Dominant Clones

- JAK2 D869G — 34.7%
- PDGFRB V523M — 46.6%
- ESR1 I326V — 50.3%

Variants of Unknown Significance (VUS)

- *EPOR* V458I — 47.2%
- *TBL1XR1* S188Y — 32.5%

Clonal Architecture



8 months

After CTX130
(9/15/2023)

Emergence of STAT3 Clone

- STAT3 P715L — 16.0%

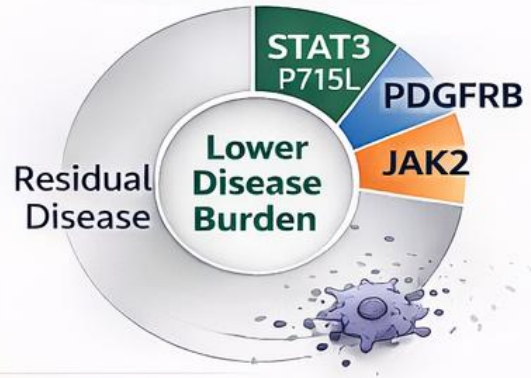
Reduced Disease Clones

- JAK2 D869G — 11.6% ↓
- PDGFRB V523M — 30.3% ↓

Residual VUS (No Major Change)

- *EPOR* V458I — 47.2%
- *ESR1* I326V — 50.3%
- *TBL1XR1* S188Y — 32.5%

Clonal Architecture



Pre-Treatment

Aggressive, Proliferative Clones

- JAK2
- PDGFRB
- ESR1

High VAFs

Post-Treatment

STAT3-Driven Indolent Clone

- STAT3 P715L

Reduced Proliferation

Lower VAF

Biological Impact of STAT3 Emergence

Clonal Shift	JAK2/PDGFRB → **STAT3**
Disease Phenotype	Aggressive → **Indolent**
Proliferation	↓ Decreased
Immune Evasion	↑ Possible

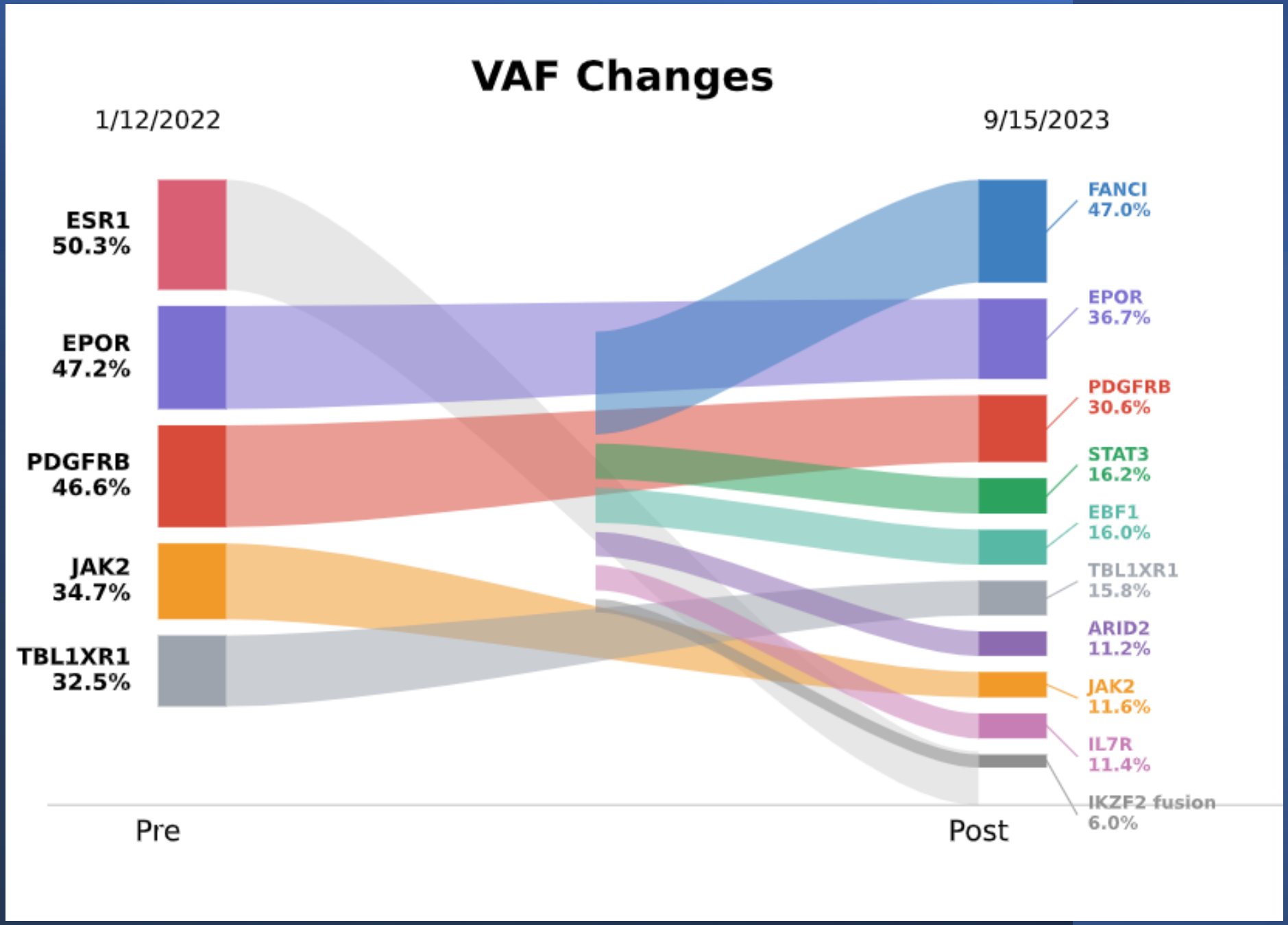
Clinical Significance

Favorable Response

- No new high-risk drivers
- Clonal control, reduced burden

Key Takeaways

- → Suppression of aggressive clones (JAK2, PDGFRB)
- → Emergence of indolent **STAT3 clone**
- → Reduced disease burden
- → **Reduced disease burden**
- → **No evidence of resistant high-risk evolution**


VAF Changes
1/12/2022
9/15/2023
ESR1
50.3%
EPOR
47.2%
PDGFRB
46.6%
JAK2
34.7%
TBL1XR1
32.5%
FANCI
47.0%
EPOR
36.7%
PDGFRB
30.6%
STAT3
16.2%
EBF1
16.0%
TBL1XR1
15.8%
ARID2
11.2%
JAK2
11.6%
IL7R
11.4%
IKZF2 fusion
6.0%
Pre
Post

ATLL COHORT: LONG-TERM SURVIVAL AND CLINICAL OUTCOMES

37.5 mo
Longest survivor in cohort

2 / 6
Alive as of February 2026

1 / 6
Bridged to AlloSCT

1
Ongoing treatment (STAT3 mutation)

Montefiore ATLL Cohort

- 7 of 9 total enrolled ATLL patients treated at Montefiore
- Historically, median OS 6-7 months in relapsed ATLL (US)
- Only 12.3% of ATLL pts had transplant access in our cohort
- CTX130 achieved disease control in a subset of patients
- Response & survival rate: best observed in multiply-relapsed ATLL
- First study of CRISPR-modified CART cells in ATLL

Why These Results Matter

- ★ ATLL predominantly affects Black, Caribbean, Hispanic communities — underserved and underrepresented in clinical trials
- ★ Off-the-shelf availability critical: aggressive ATLL cannot wait weeks for autologous manufacturing
- ★ Genomic insights may identify patients who can benefit from CAR T → AlloSCT consolidation strategy
- ★ STAT3 acquisition: opens possibility of immune editing toward less aggressive phenotype

CONCLUSIONS & FUTURE DIRECTION

- ✓ CTX130 is the FIRST CRISPR-modified, allogeneic CAR T therapy studied in ATLL — with manageable safety (no GvHD) and promising efficacy
- ✓ At optimal doses (DL3+): 51.6% ORR and 19.4% CR in the broader TCL cohort; ATLL subgroup 55% ORR and 33% CR
- ✓ CTX130 served as a bridge to allogeneic SCT in 1/6 ATLL patients — filling a critical treatment gap in a population with no established salvage options
- ✓ Genomic profiling reveals ATLL clonal plasticity under CAR T pressure — STAT3 acquisition may indicate immune editing toward more indolent phenotype (Longest Survivor: 37.5 Months)

REFERENCES & ACKNOWLEDGMENTS

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All patients and their families

CRISPR Therapeutics & CRSP-ONC4 Clinical Trial Team

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All Clinical Trial Office members

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Latoya Townsend

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Key Publications

1. Iyer SP, Sica RA, Ho PJ, et al. Safety and activity of CTX130, a CD70-targeted allogeneic CRISPR-Cas9-engineered CAR T-cell therapy in patients with R/R T-cell malignancies (COBALT-LYM). Lancet Oncol. 2025;26(1):110-122.

2. Cordover E, Sica RA et al. First-in-human study of CTX130 in ATLL: Clinical and genomics findings from long-term follow-up of COBALT-LYM Phase 1 trial. Blood. 2025;146(Supplement 1):4143.

3. Shah UA, et al. Incidence of ATLL in the US (2001–2015 NPCR). Cancer. 2020;126:567-574.

4. Watanabe T. Adult T-cell leukemia: molecular basis for clonal expansion and transformation of HTLV-1-infected T cells. Blood. 2017;129:1071-1081.

5. Cook LB, Phillips AA. How I treat adult T-cell leukemia/lymphoma. Blood. 2021.

Thomas Jefferson University | Drexel University | Drexel Medicine

22nd International Conference on Human Retrovirology:
HTLV and Related Retroviruses
HTLV2026

June 3-6, 2026 | Philadelphia, Pennsylvania, USA

Venetoclax-Based Therapy in Relapsed/Refractory North American Adult T-Cell Leukemia/Lymphoma

Ankit Tanwar, Ph.D.
(Staff Scientist)

EINSTEIN
Albert Einstein College of Medicine

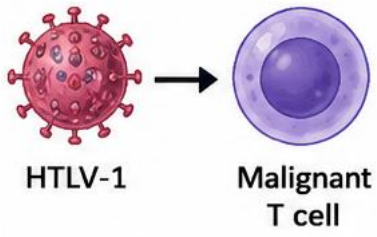
Montefiore Einstein
Comprehensive Cancer Center

Conflicts of interest:

I have no conflicts of interest

Background & Clinical Significance

Adult T-Cell Leukemia/Lymphoma (ATLL)



- ❑ HTLV-1 driven aggressive mature $CD4^{+}$T-cell malignancy
- ❑ Distinct and highly refractory disease in North American patients
- ❑ Poor prognosis despite multimodal therapy
- ❑ Limited targeted therapeutic options

Historical Outcomes

Median Survival:

~6–9 months

Response Rate:

~30%

(especially in relapsed/refractory disease)

Why Venetoclax in NA-ATLL?

- ✓ Venetoclax is a highly selective BCL-2 inhibitor *(FDA approved, 2016)*
- ✓ Clinically effective in multiple hematologic malignancies (CLL, AML)
- ✓ NA ATLL cells has high BCL-2 expression and TP53, NOTCH1 mutation, may depend on anti-apoptotic signaling pathways *(Tanwar et al., 2024, Blood)*
- ✓ Targeting mitochondrial apoptosis may represent a therapeutic vulnerability

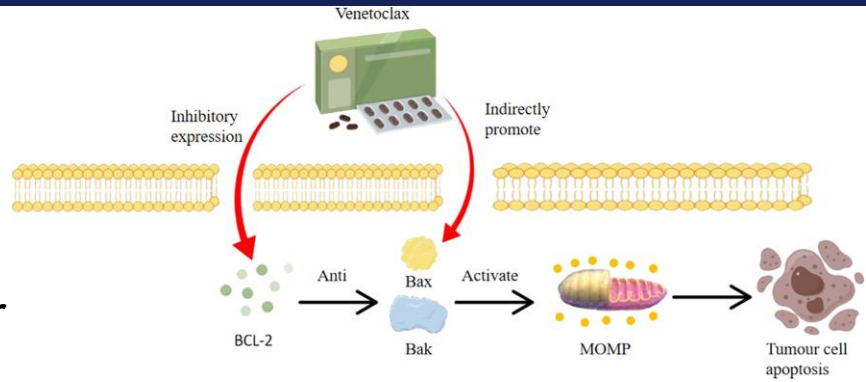


Image1: Generalized Venetoclax mechanism

Hypothesis:

Venetoclax alone or in combination with antiviral therapy may improve responses in NA-ATLL.

Experimental Platform & Study Design

Pre-clinical Study

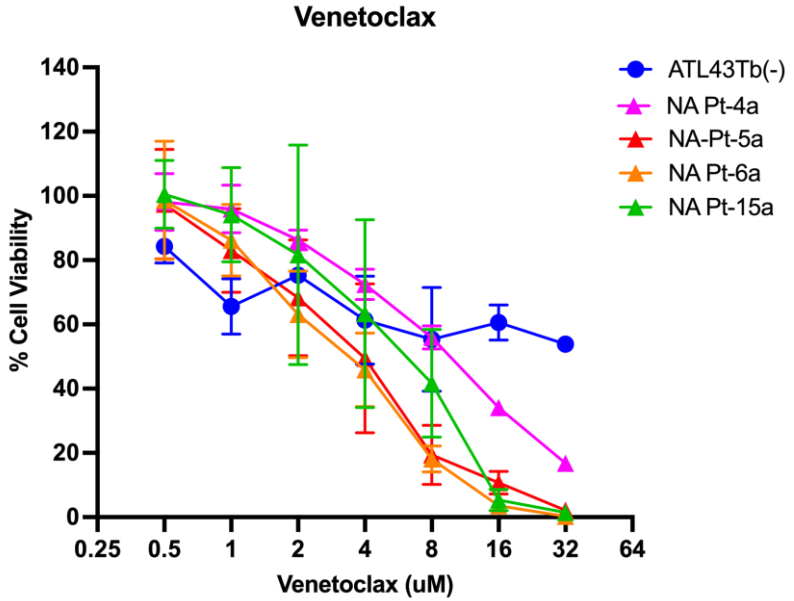
- NA-ATLL patient-derived cell lines
- Primary ATLL samples
- Cell viability assays
- Apoptosis studies
- RNA-sequencing and pathway analysis
- Notch glycosylation

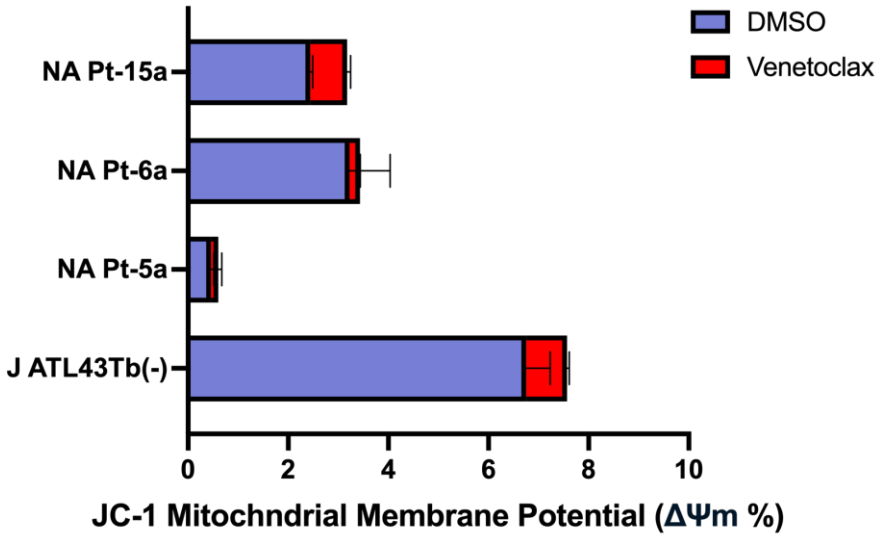
Clinical Study

- 7 relapsed/refractory NA-ATLL patients *(Shimoyama classification)*
- Venetoclax-based therapeutic strategies as per the institute proposed treatment algorithm
- HTLV-1 viral load evaluation
- Clinical response monitoring

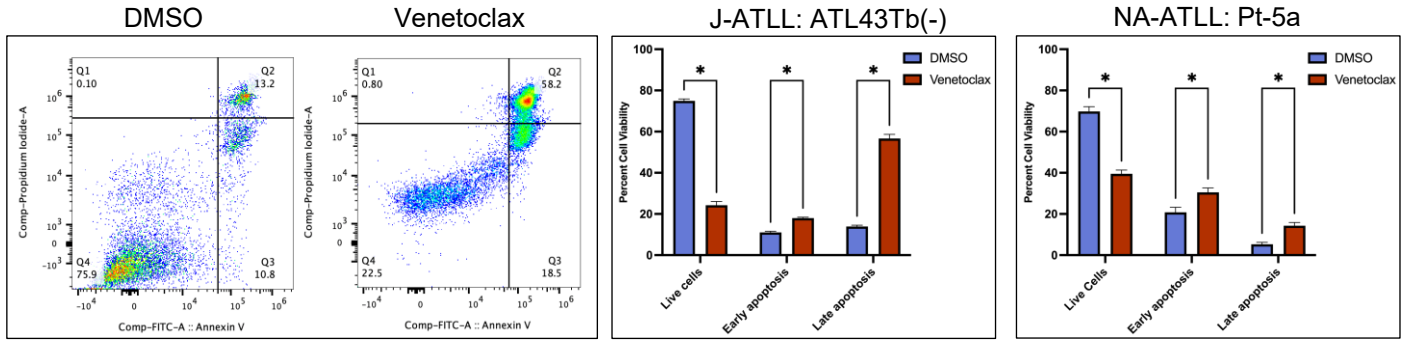
Integrated Translational Approach: Combining Preclinical Modeling with Early Clinical Investigation in NA-ATLL

Venetoclax shows strong preclinical activity

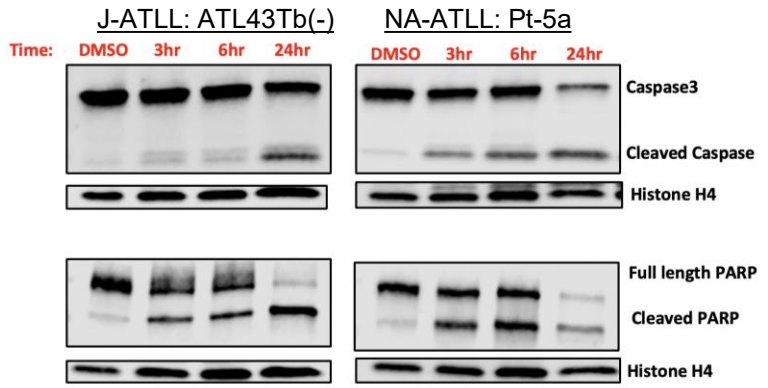




Flow Representation: Annexin V/PI



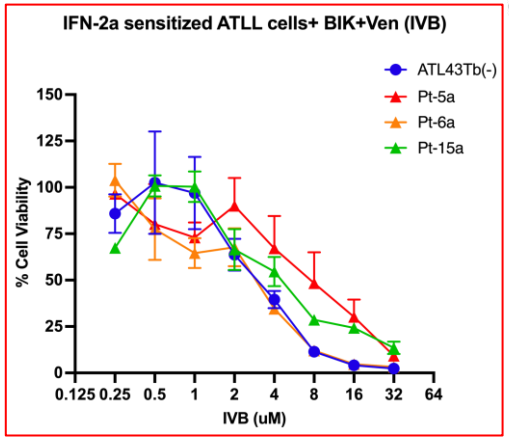
Dynamics of apoptosis (Rapid activation/degradation)



#Strong rationale for Venetoclax-based combination therapy

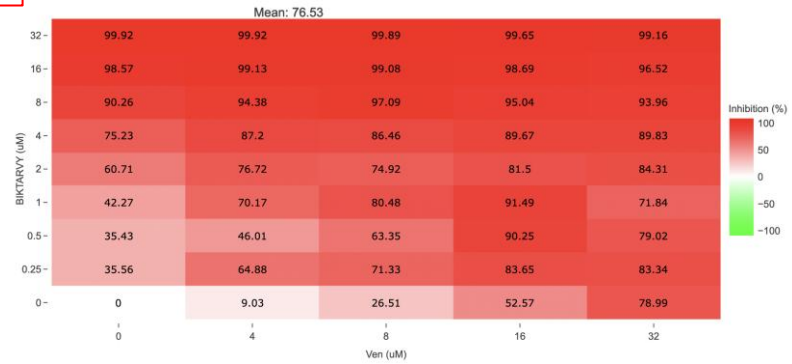
Venetoclax based combination therapy: PEG-IFN2a/Biktarvy

J-ATLL



Synergy: Ven/BIK

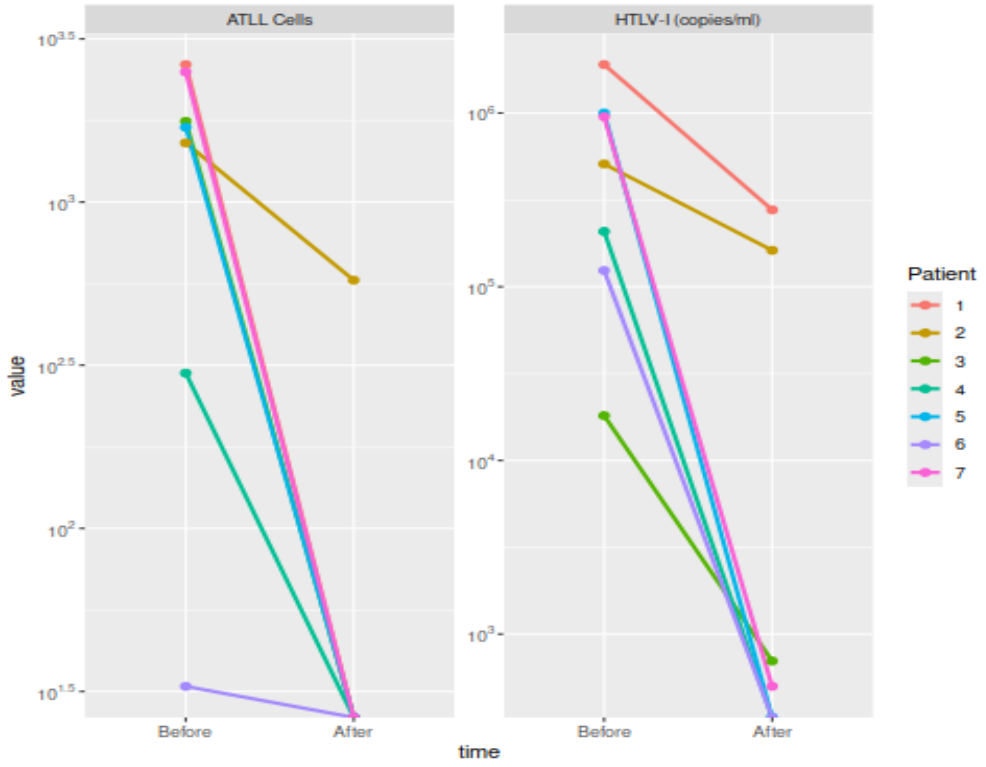
NA-ATLL



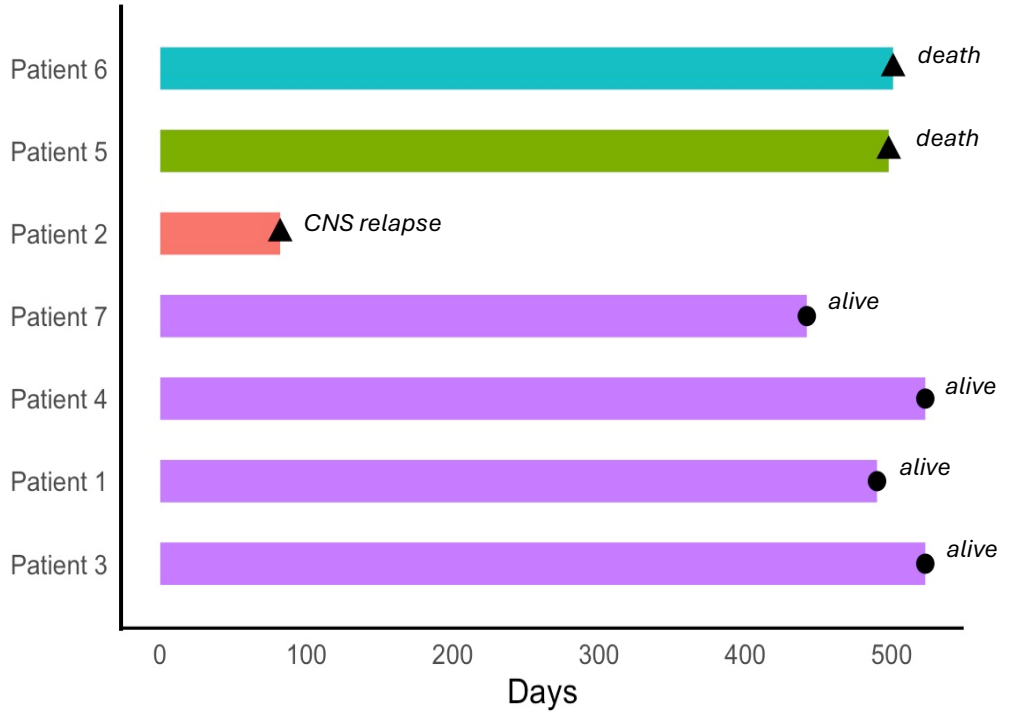
IVB: Venetoclax with PEG-IFNα2a and Biktarvy

Early Clinical Observations: Venetoclax/PEG-IFN2a/Biktarvy

Paired before-after plot



Swimmer plot of clinical outcomes



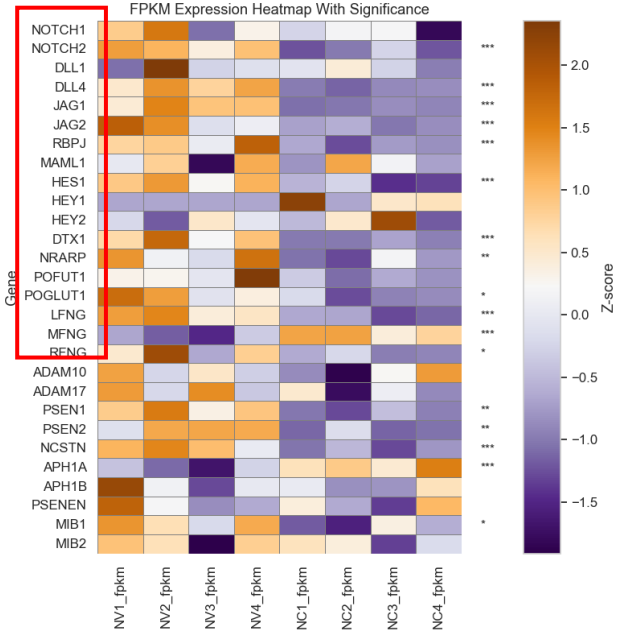
Although preliminary, our clinical observations support further exploration of Venetoclax-based combination therapy in NA-ATLL

Montefiore Einstein: Dr. Sica Study

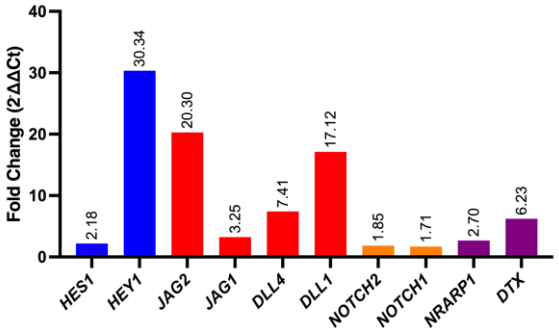
Manuscript under revision (Tanwar & Sica et al., Blood)

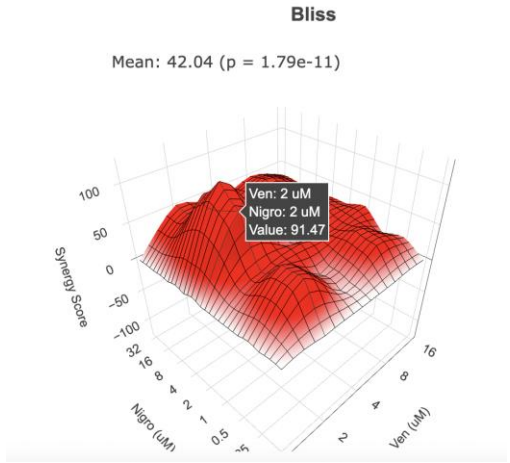
Adaptive Resistance Mechanisms: Limit long-term Venetoclax responses

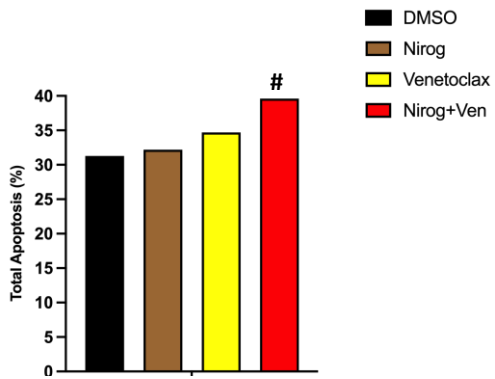
RNA Seq: NA ATLL



Synergistic Impact: Venetoclax + Nirogcaestat







Take-Home Messages

1. *Venetoclax shows promising activity in NA-ATLL*
2. *Combination therapy (VEN/IFN/BIK) enhances anti-tumor effects*
3. *Early clinical observations are encouraging*
4. *Adaptive signaling pathways may mediate resistance*
5. *Rational combinations warrant further investigation*

"Our work supports Venetoclax-based combination therapy as a promising translational strategy for relapsed/refractory North American ATLL."

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All patients and their families

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- ❑ Pamela Stanley, Ph.D.

Einstein Core Facilities

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HTLV2026

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Adult T cell Leukaemia/Lymphoma: Survival in the UK in 2025

Anna Weatherill, Wang Guo, Patricia Watber, Anat Melamed, Clare Greiller, Graham P Taylor, Aileen Rowan, Lucy Cook

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NHS
Imperial College Healthcare
NHS Trust

NATIONAL CENTRE FOR HUMAN RETROVIROLOGY
LONDON, UNITED KINGDOM

Background

- 3-5% HTLV carriers will develop ATL
- Shimoyama criteria (1991) define acute, lymphoma, chronic and smoldering subtypes
- Median OS 8 and 10 months for acute and lymphoma subtypes, respectively, in ATL cohort diagnosed 1999-2009 in England (Hodson et al, 2011).
- Overall survival has not changed since ATL first described 40 years ago

Table I. Diagnostic criteria for clinical subtype of ATL

	Smouldering	Chronic	Lymphoma	Acute
Anti-HTLV-1 antibody	+	+	+	+
Lymphocyte ($\times 10^9$/l)	<4	≥4[a]	<4	*
Abnormal T-lymphocytes	≥5%	+[b]	≤1%	+[b]
Flower cells of T cell marker	Occasionally	Occasionally	No	+
LDH	≤1·5N	≤2N	*	*
Corrected Ca (mmol/l)	<2·74	<2·74	*	*
Histology—proven lymphadenopathy	No	*	+	*
Tumour lesion				
Skin	**	*	*	*
Lung	**	*	*	*
Lymph node	No	*	Yes	*
Liver	No	*	*	*
Spleen	No	*	*	*
CNS	No	No	*	*
Bone	No	No	*	*
Ascites	No	No	*	*
Pleural effusion	No	No	*	*
GI tract	No	No	*	*

N, normal upper limit; GI, gastrointestinal.

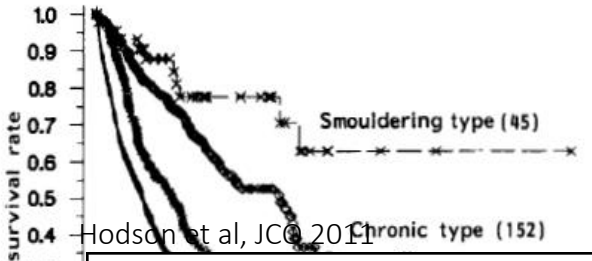
* No essential qualification except terms required for other subtype(s). ** No essential qualification if other terms are fulfilled, but histology-proven malignant lesion(s) is required in case abnormal T-lymphocytes are less than 5% in peripheral blood.

[a] Accompanied by T-lymphocytosis ($3·5 \times 10^9$/l or more). [b] In case abnormal T-lymphocytes are less than 5% in peripheral blood, histology-proven tumour lesion is required.

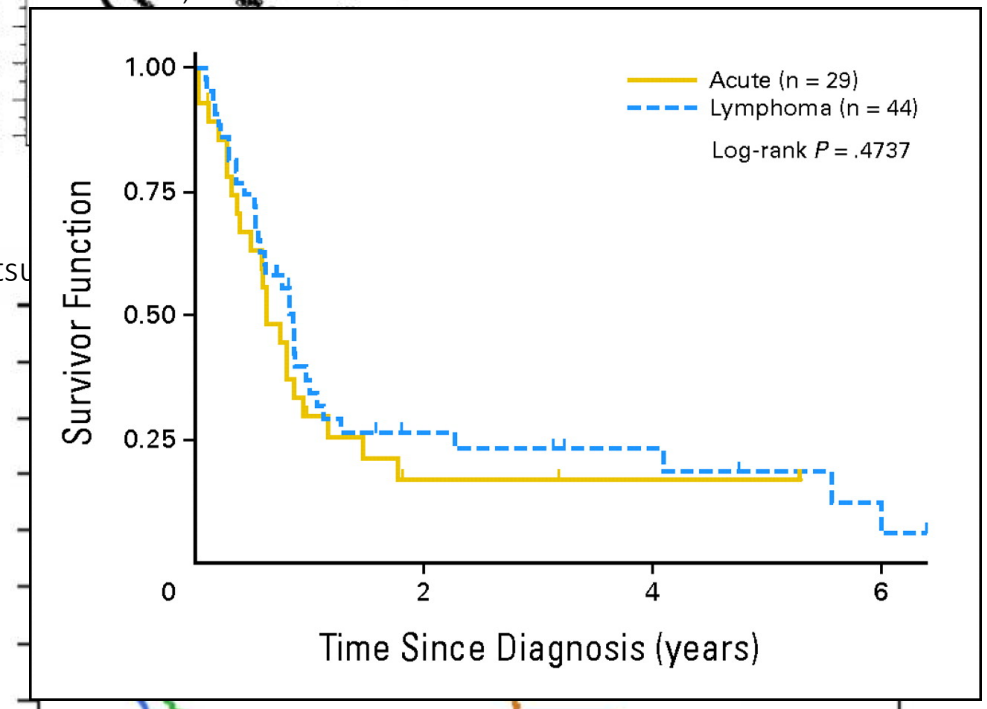
Background

- 3-5% HTLV carriers will develop ATL
- Shimoyama criteria (1991) define acute, lymphoma, chronic and smoldering subtypes
- Median OS 8 and 10 months for acute and lymphoma subtypes, respectively, in ATL cohort diagnosed 1999-2009 in England (Hodson et al, 2011).
- Overall survival has not changed since ATL first described 40 years ago

Shimoyama et al, BJH 1991



Hodson et al, JCO 2011



Katsu

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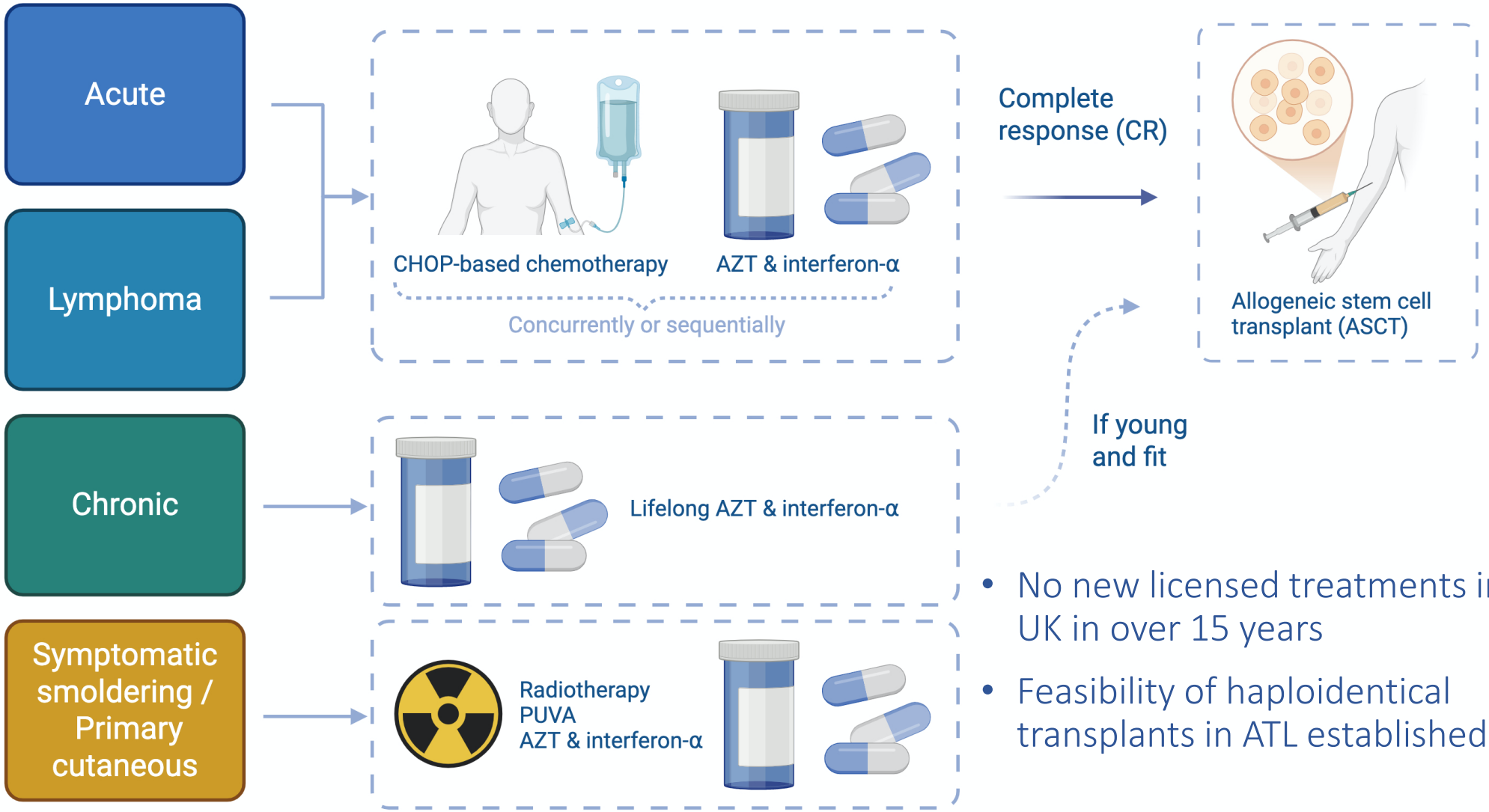
Treatment approach



- No new licensed treatments in the UK in over 15 years
- Feasibility of haploidentical transplants in ATL established ~2020

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Our study

NATIONAL CENTRE FOR HUMAN RETROVIROLOGY
LONDON, UNITED KINGDOM

National registry of ATL patients at the HTLV clinic, National Centre for Human Retrovirology, St Mary's Hospital

ATL diagnosed between 1/1/10 and 31/12/24, inclusive

Minimum data requirement:

- ATL subtype
- Date of birth
- Date of diagnosis
- Date of death or last follow-up

Subgroup analysis:

Targeted deep sequencing on diagnostic PBMC samples of 50 patients

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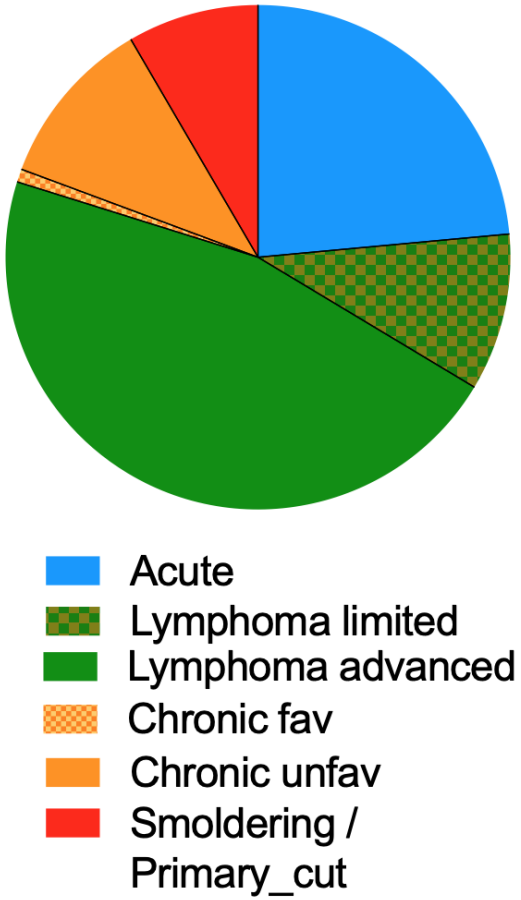
Baseline characteristics



Characteristic	Number (%), n=119
Female	59 (49.6)
Age at diagnosis in years, median (range)	56 (26-85)
Black Caribbean ethnicity	77 (64.7)
Follow up time in months, median (range)	
Alive	49.8 (3.4-180.1)
Dead	8.6 (1.1-100)
Patients dead at censor date	82 (68.9)
ATL subtype	
Acute	28 (23.5)
Lymphoma	67 (56.3)
Limited stage (I/II)	*12*
Advanced stage (III/IV)	*55*
Chronic	14 (11.8)
Favourable	*1*
Unfavourable	*13*
Smoldering / Primary cutaneous	10 (8.4)

Clinical characteristics

Characteristic	Number of patients (%)
Blood borne infection	
Hepatitis B (core antibody positive)	30/108 (27.8)
Active infection	*3*
Previous infection	*27*
Hepatitis C	1/103 (1.0)
Human Immunodeficiency Virus (HIV)	4/101 (4.0)
Syphilis (serology positive)	7/96 (7.3)
Strongyloides	
Strongyloides serology positive	12/106 (11.3)
Symptomatic strongy at diagnosis	2
Other HTLV related morbidity	
HAM/TSP	5/113 (4.4)
Uveitis	6/113 (5.3)
Seronegative arthritis	3/113 (2.7)

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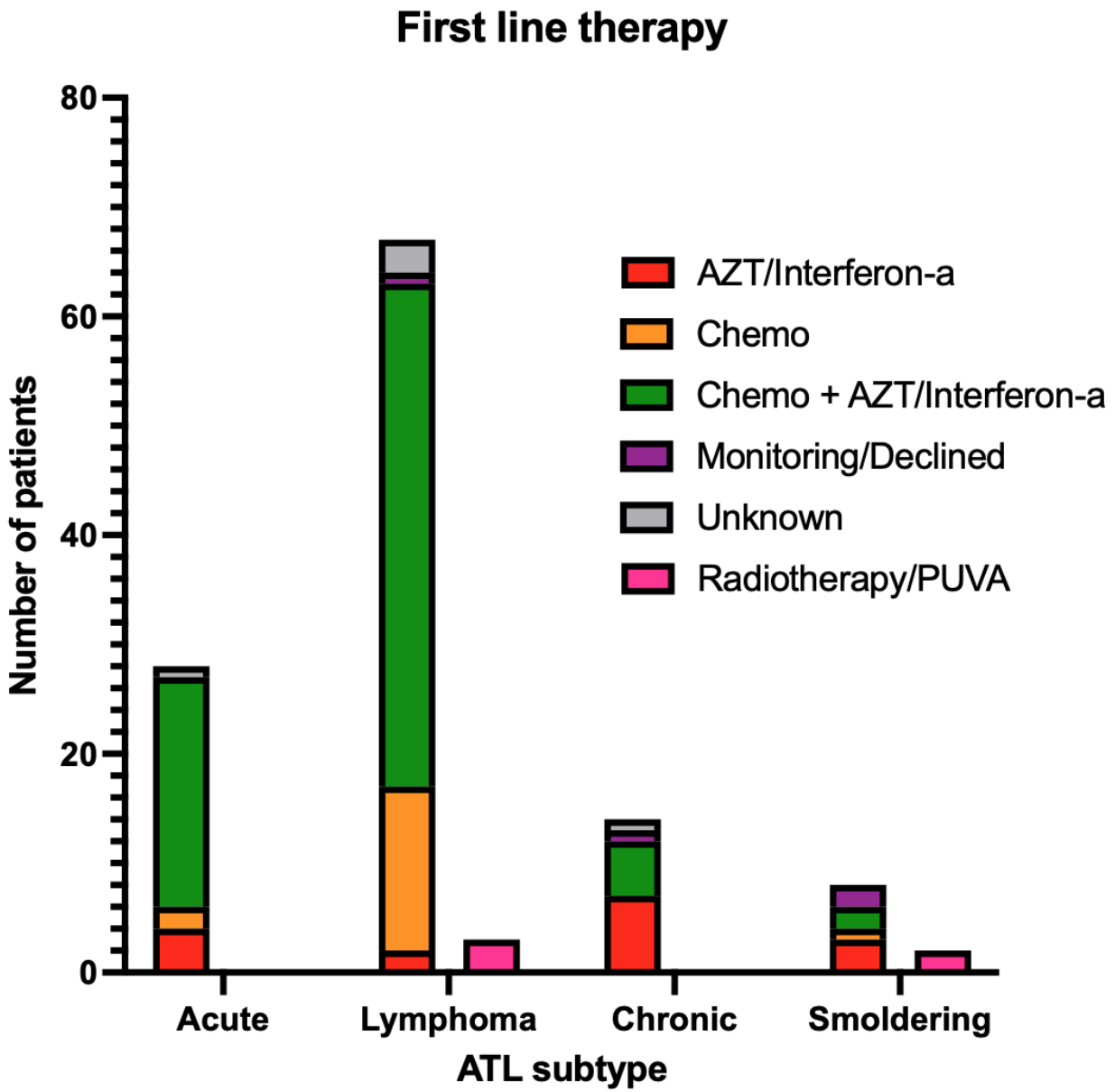
First line treatment



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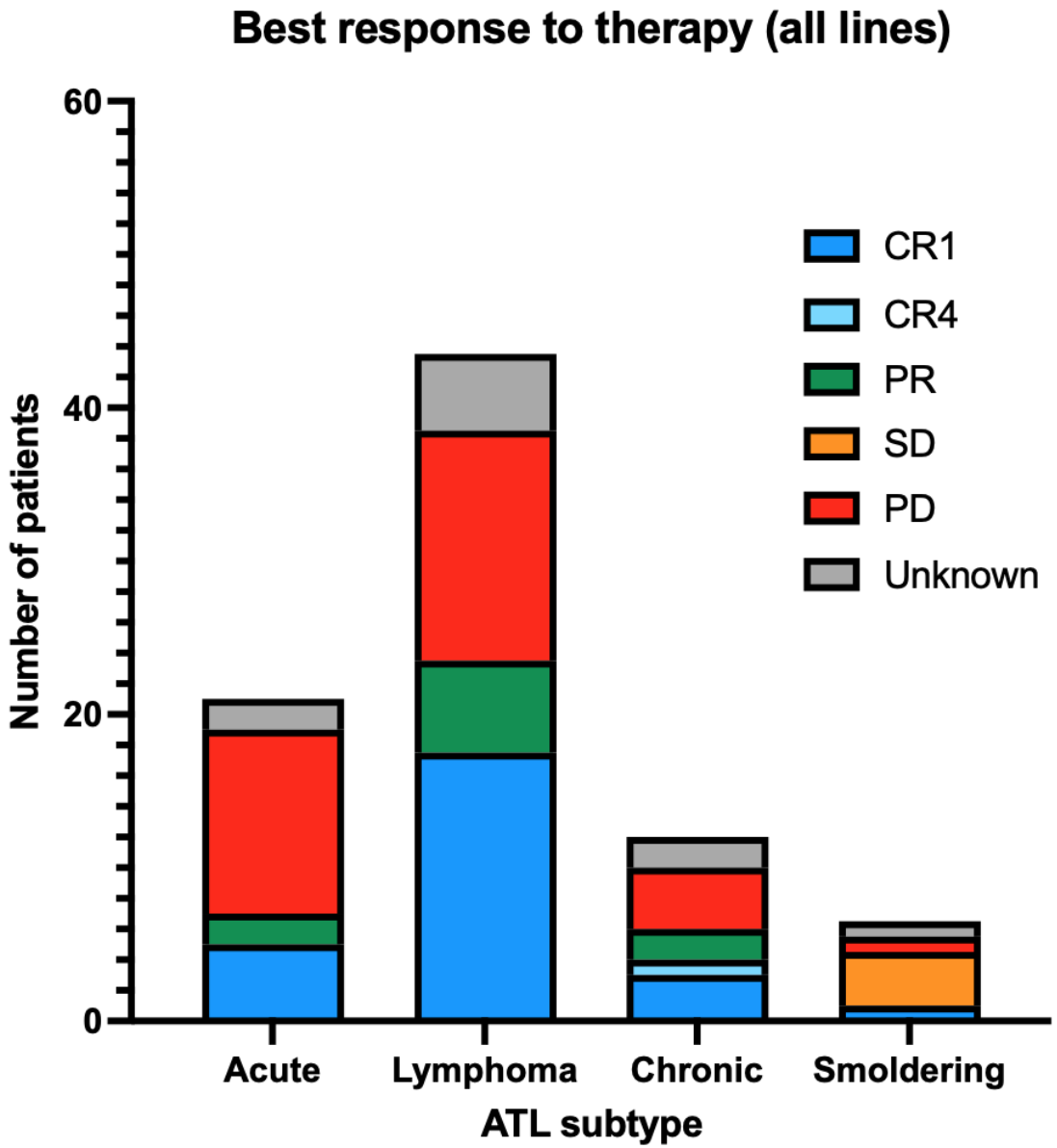
Best response to therapy

- Lymphoma was the most chemotherapy-sensitive subtype
- High rates of chemotherapy refractoriness in acute and lymphoma subtypes



Allogeneic stem cell transplant (ASCT)

28 (23.5%) patients underwent ASCT

Pre-"Haplo era"
(diagnosed 1/1/10- 1/6/17)

6/48 (12.5%)

"Haplo era"
(diagnosed 1/6/17-31/12/24)

22/71 (31.0%)
16/22 (72.7%) haploidentical

Characteristic, n=28	Number of transplanted patients (%)	Number deceased (%), n=15 (53.6)
ATL subtype		
Acute	6 (21.4)	5/6 (83.3)
Lymphoma	19 (64.3)	10/19 (52.6)
Limited stage (I/II)	2	0
Advanced (III/IV)	17	10/17 (58.8)
Chronic aggressive	2 (7.1)	0
Primary cutaneous	1 (3.4)	0
Transplant type		
Haplo	16 (57.1)	8/16 (50)
Non-haplo	12 (42.3)	7/12 (58.3)
Disease status at time of transplant		
CR1		
CR4	24 (85.7)	14/24 (58.3)
PR	1 (3.6)	0
SD	2 (7.1)	1/2 (50)
	1 (3.6)	0
HTLV-1 positive donor	2 (7.1)	0
Integrase inhibitor administration (raltegravir)	16 (57.1)	8/16 (50)
Cause of death, n=15		
Progressive disease		**10 (66.7)**
Transplant complications		**4 (26.7)**
Therapy related AML		**1 (6.7)**

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Overall survival by ATL subtype

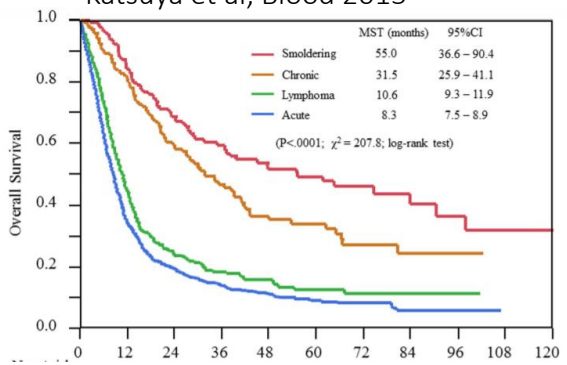
Acute median OS 7.6 months (4.3-9.0 95% C.I.), 2-year OS 22.5%

Lymphoma mOS 15.8 months (8.9-21.9 95% C.I.) 2-year OS 35.7%

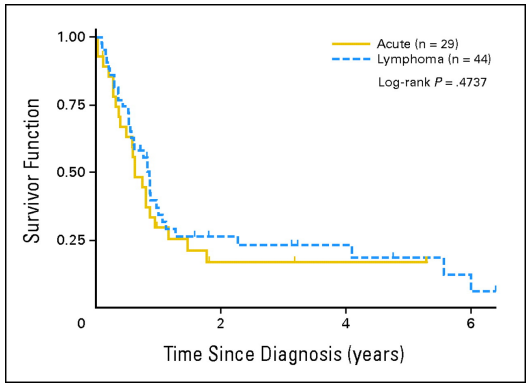
Chronic mOS 77.3 months (10.9- 95% C.I.), 2-year OS 70.1%

Smoldering mOS not reached, 2-year OS 88.9%

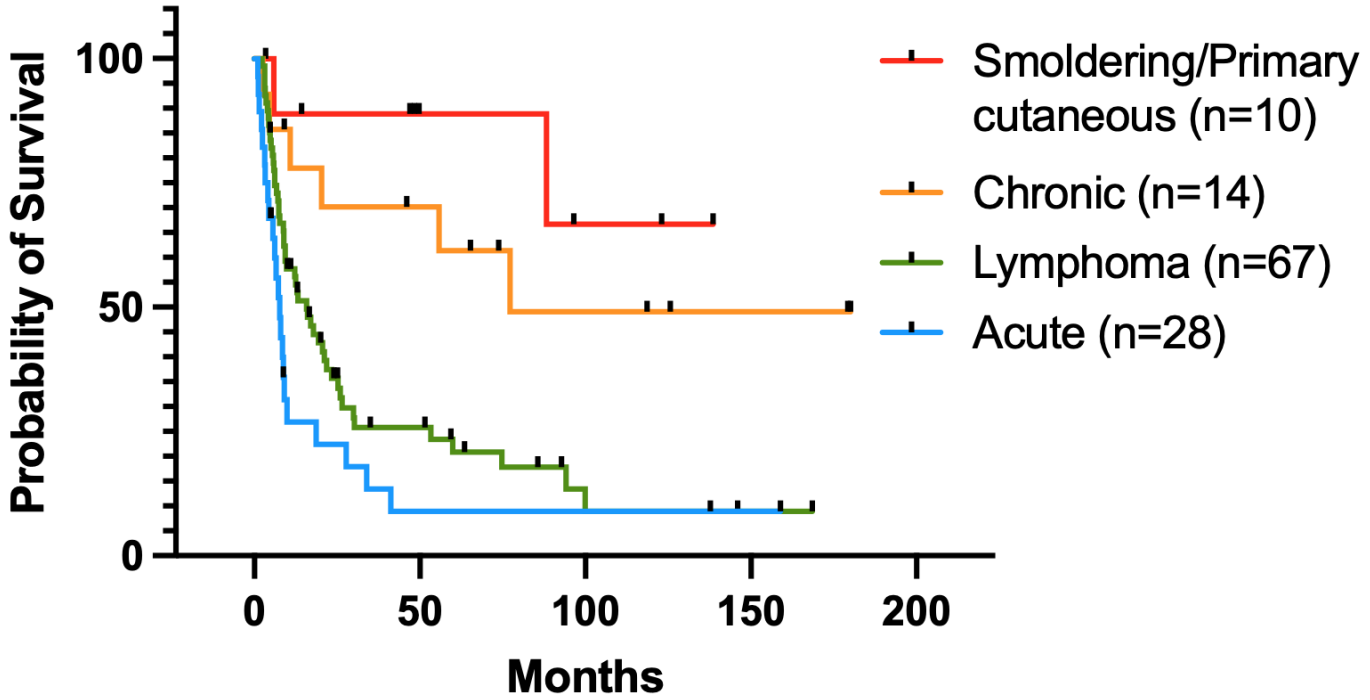
Katsuya et al, Blood 2015



Hodson et al, JCO 2011



OS by ATL subtype



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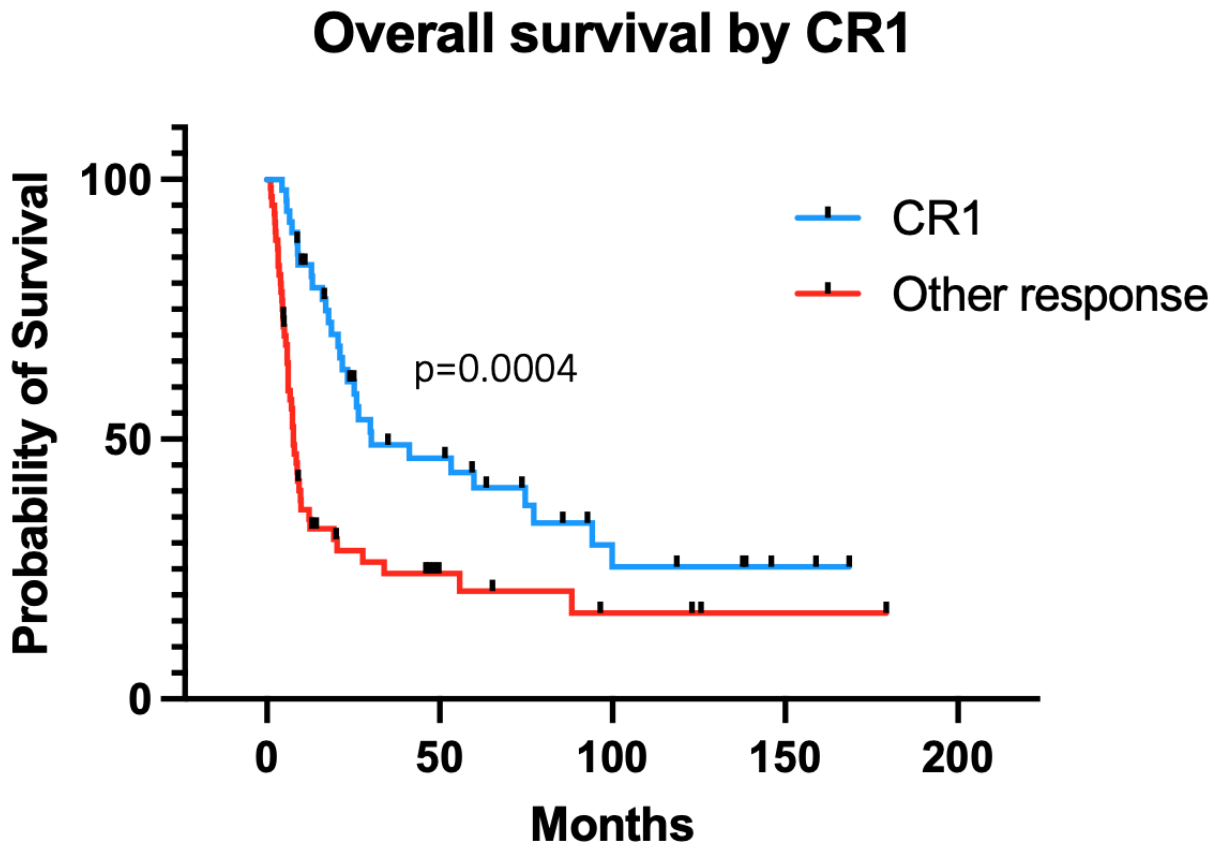
CR1 associated with significantly improved survival

- Median survival CR1 group 30.2 months (21.9-77.3 95% C.I.) vs other response group 7.6 months (6.2-9.8 95% C.I.)

- Mortality HR in non-CR1 group compared to CR1 group 2.328 (1.458-3.716 95% C.I.)



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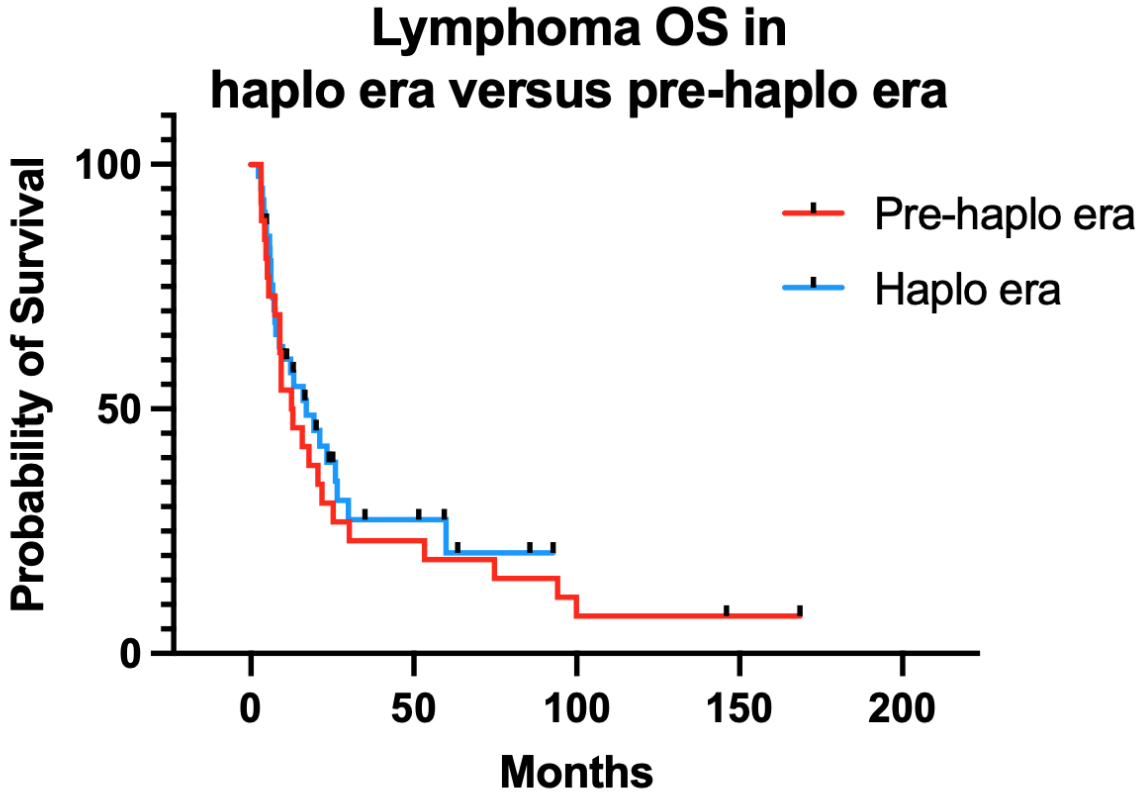
Lymphoma survival in the haploidentical transplant era

- Median OS in pre-haplo era vs haplo era 12.7 months (7.4-21.9 95% C.I.) vs 17.0 months (7.6-26.5 95% C.I.), respectively (not statistically significant)
- 2-year overall survival 30.8% vs 39.1%
- Perhaps too soon to say



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Cause of death

Chemotherapy refractory ATL and relapse were the main cause of death

Cause of death (n=82)	Number of patients (%)
ATLL	73 (89.0)
Transplant related complications	5 (6.1)
Secondary AML (ATL in CR)	1 (1.2)
Fungal LRTI (with ATL in CR)	1 (1.2)
Old age / frailty	1 (1.2)
Unknown, off treatment	1 (1.2)

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Are somatic ATL driver mutations associated with clinical outcomes?

- Dr Aileen Rowan's group have developed a panel of 42 genes commonly mutated in ATL, based on the international literature (Kogure Y, Kataoka K, Cancer Science 2017).
- 50 frozen PBMC samples from 50 patients taken at diagnosis before, or within 28 days of, first line treatment initiation.
- Deep targeted sequencing using the gene panel, and results were reviewed alongside clinical outcomes.

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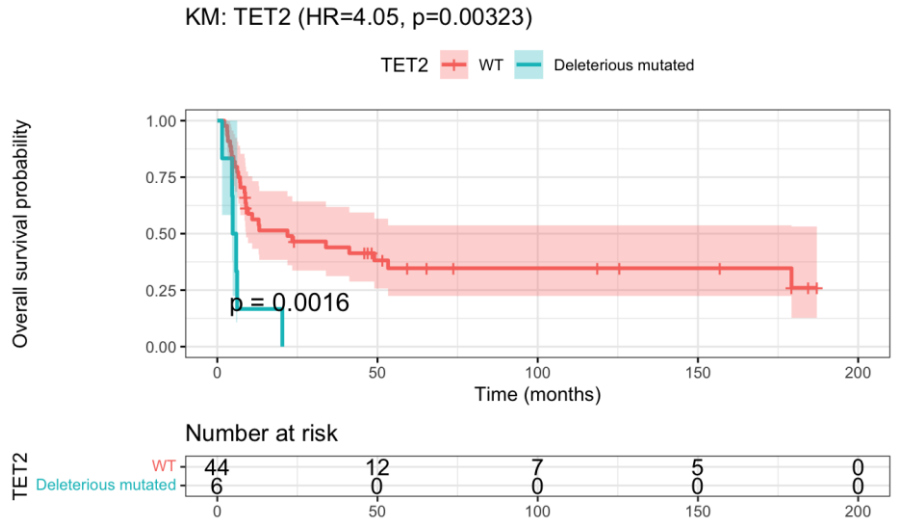
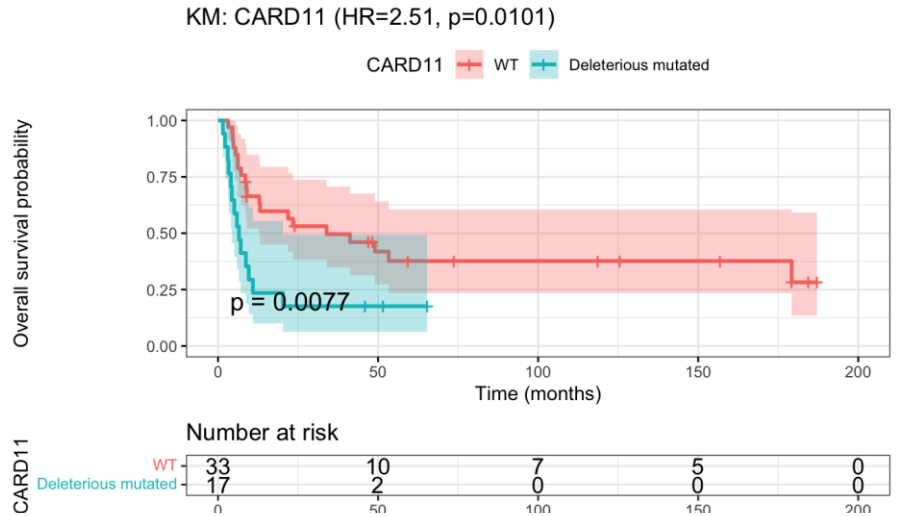
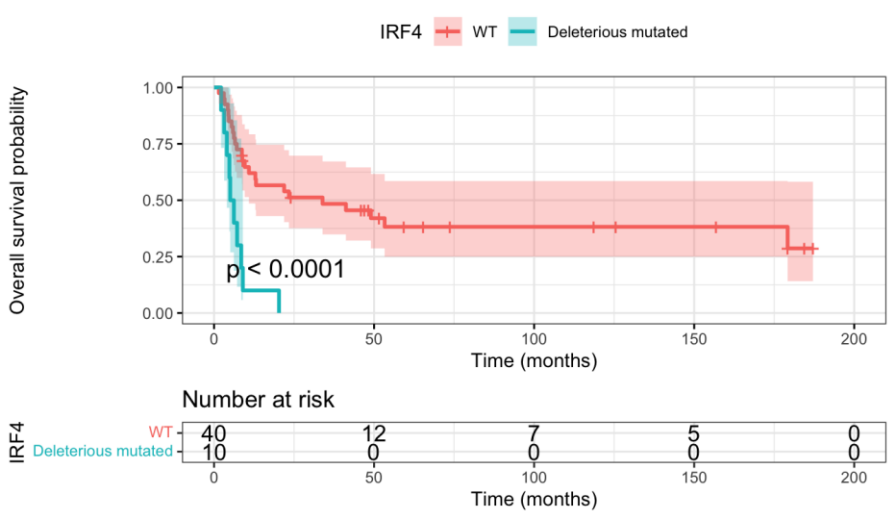
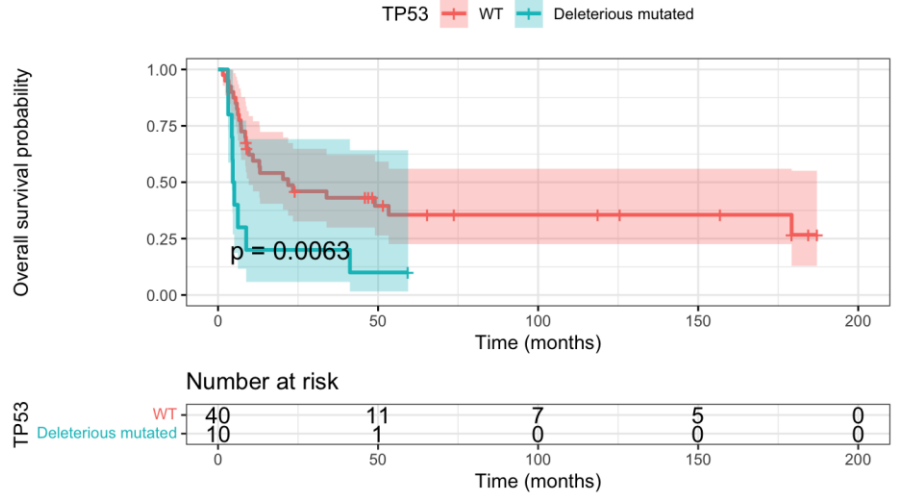
Deleterious variants in TET2, CARD11, IRF4 and TP53 were associated with inferior survival.









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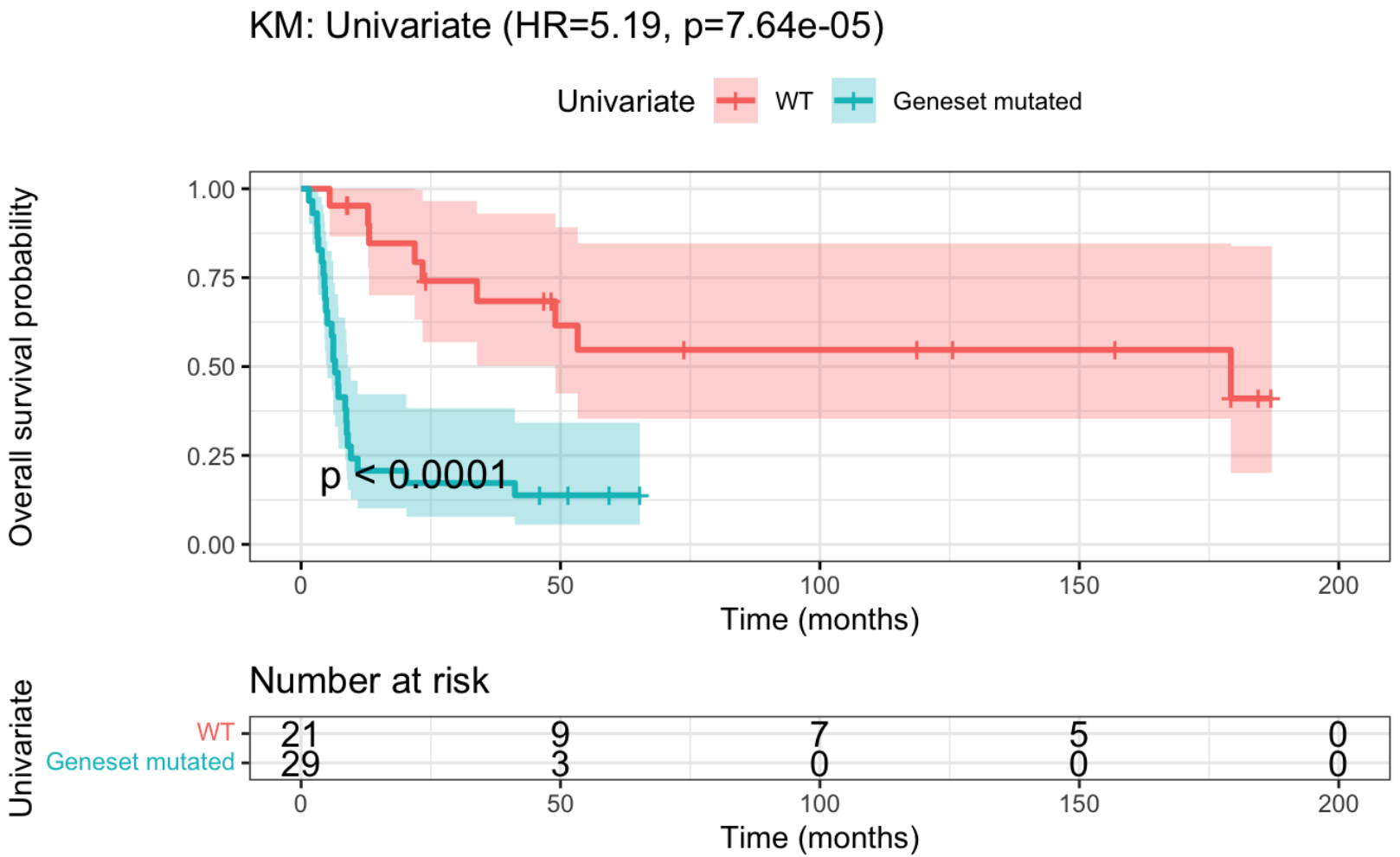
If we separate patients with variants in IRF4, TET2, TP53 and/or CARD11, we start to be able to separate out people with poorer prognosis.



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Conclusions and future direction

- Outcomes of aggressive subtypes of ATL remain poor, with **high rates of primary refractoriness** to chemotherapy and **relapse**.
- Median survival in **chronic ATL was 77.3 months** which is longer than in previous studies. We attribute this to greater use of **antivirals upfront**, and even chemotherapy and ASCT in some cases.
- In chemotherapy sensitive disease, use of **haploidentical ASCT** has improved accessibility to the only curative treatment – this is reflected in **increased transplant rates.** It is too soon to comment on survival benefit.
- **Achieving CR1** was associated with longer survival.
- Presence of **mutations in TP53, IRF4, TET2 and/or CARD11** was associated with shorter survival.
- To improve ATL outcomes, we need to establish the **mechanisms of treatment refractoriness** and develop **novel therapies** that directly address these mechanisms.
- But perhaps a more realistic approach would be to use existing therapies in a characterized high risk carrier population, to **prevent ATL from developing in the first place.**

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22nd International Conference on Human Retrovirology:
HTLV and Related Retroviruses
HTLV2026

June 3-6, 2026 | Philadelphia, Pennsylvania, USA

Immunological biomarkers in people with HTLV-1 treated with Dolutegravir

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Immunological Biomarkers in People with HTLV-1 Treated with Dolutegravir

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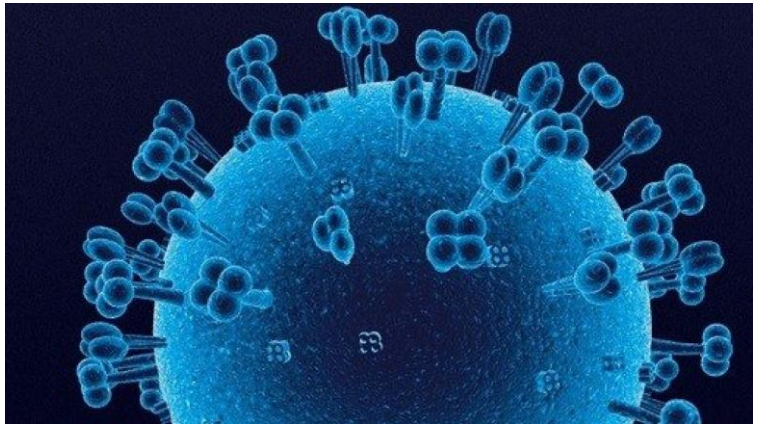
Fundação Bahiana de Infectologia
Salvador, Brazil

Brites C, Montaño-Castellon I, Marconi C, Mayoral R, Luz E, Figueredo CA, Fiuza BSD, Netto EM

Philadelphia, June 3-6, 2026

Background



HTLV-1 and immune dysregulation

HTLV-1 infection drives chronic immune activation, with dysregulated cytokine networks linked to viral persistence and disease progression (HAM/TSP, ATLL).

No approved antiviral therapy

No specific treatment currently exists for HTLV-1. Management has focused on symptom relief, not viral control.

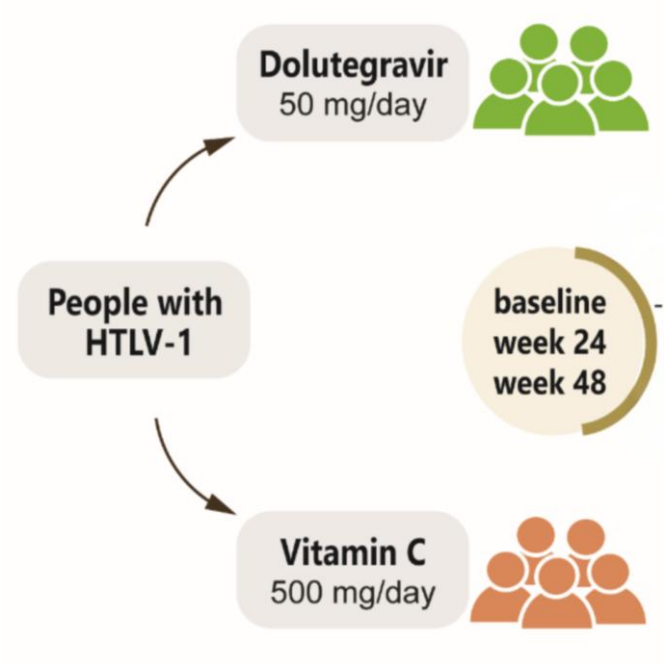
Dolutegravir (DTG) as a candidate

DTG, a second-generation integrase inhibitor used in HIV treatment, targets viral integration — a central mechanism in HTLV-1 persistence. A phase 2 trial showed DTG reduced HTLV-1 proviral load (PVL) significantly.

Starling AL, et al. Immunological signature of the different clinical stages of the HTLV-1 infection: establishing serum biomarkers for HTLV-1-associated disease morbidity. Biomarkers. 2015;20(6-7):502-512.
Futsch N et al. Cytokine Networks Dysregulation during HTLV-1 Infection and Associated Diseases. Viruses. 2018 Dec 5;10(12):691

Study Design

Phase 2, Double-Arm Randomized Controlled Trial



The study was conducted at Fundação Bahiana de Infectologia, In Salvador, capital of Bahia state, Brazil.

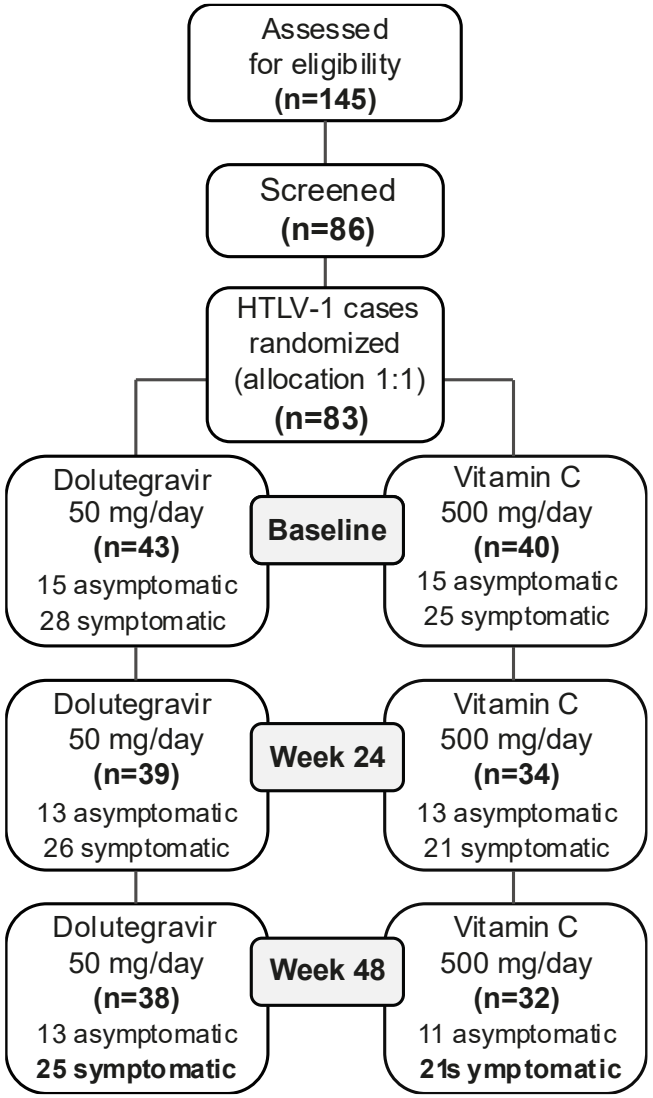
Cytokine subset
n=25 (PVL >78 copies/mL)

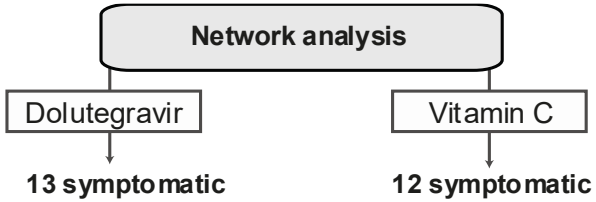
IL-2, IL-4, IL-6, IL-10,
TNF-α, IFN-γ, IP-10, MIP-1α

Immunological Aim

To evaluate changes in plasma cytokine and chemokine levels (IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ, IP-10, MIP-1α) and cytokine network architecture in people with HTLV-1 treated with dolutegravir compared to vitamin C over 48 weeks.

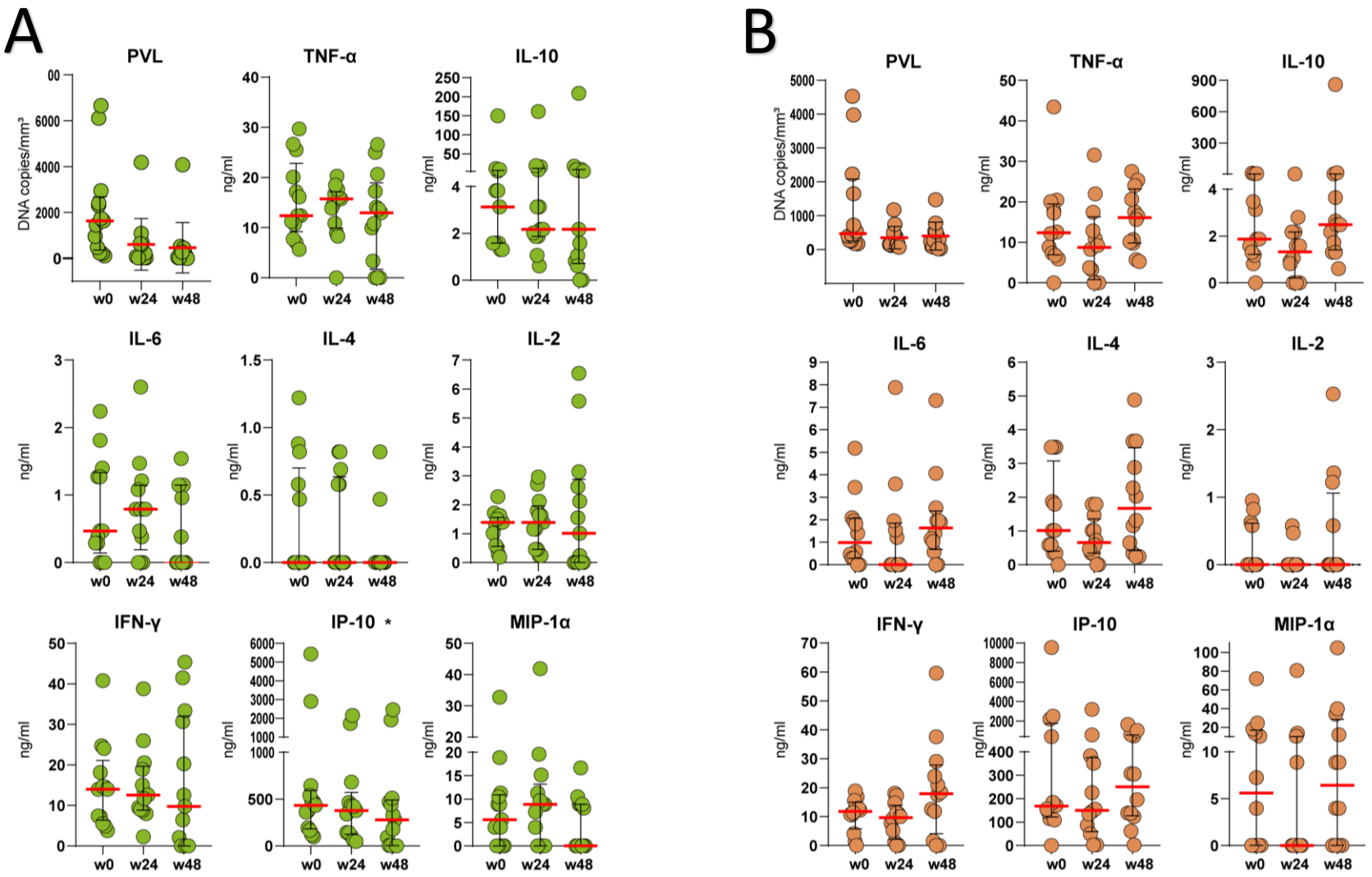
Participants





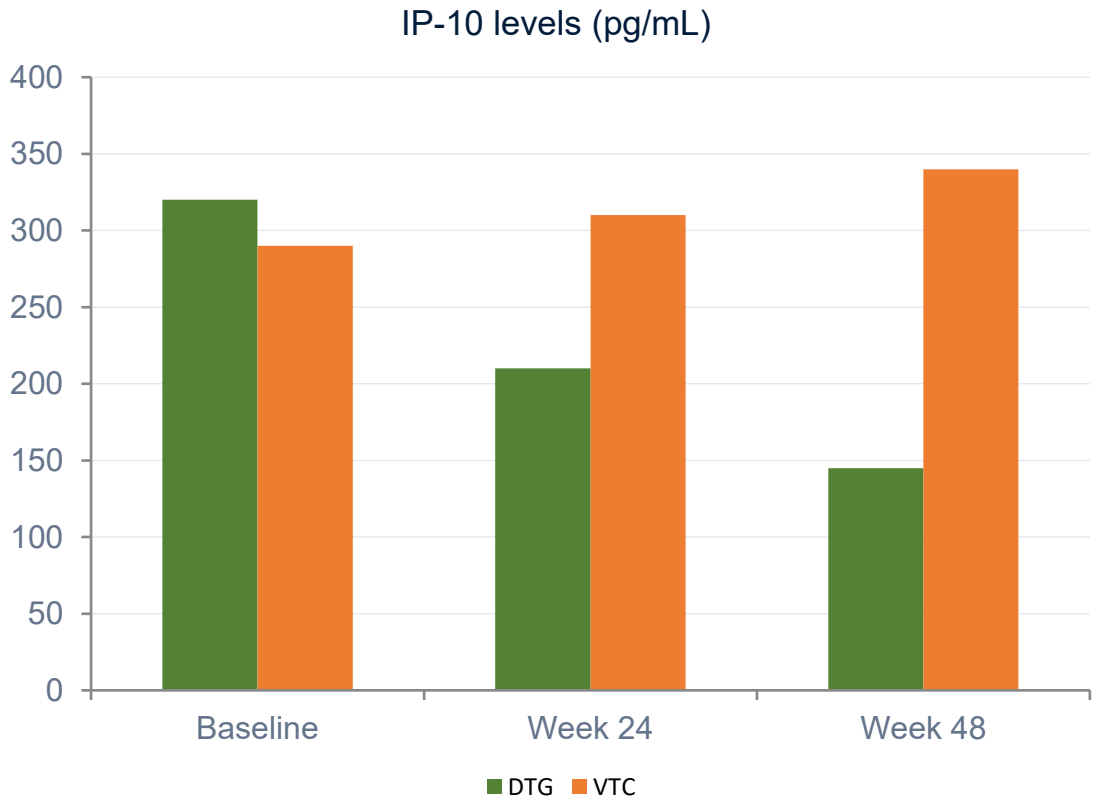
Characteristic	DTG (n=13)	VTC (n=12)	p-value
Age, median (IQR)	47.5 (46.2–53.8)	51.0 (43.8–54.5)	0.692
Female sex, n (%)	13 (100%)	9 (75%)	0.192

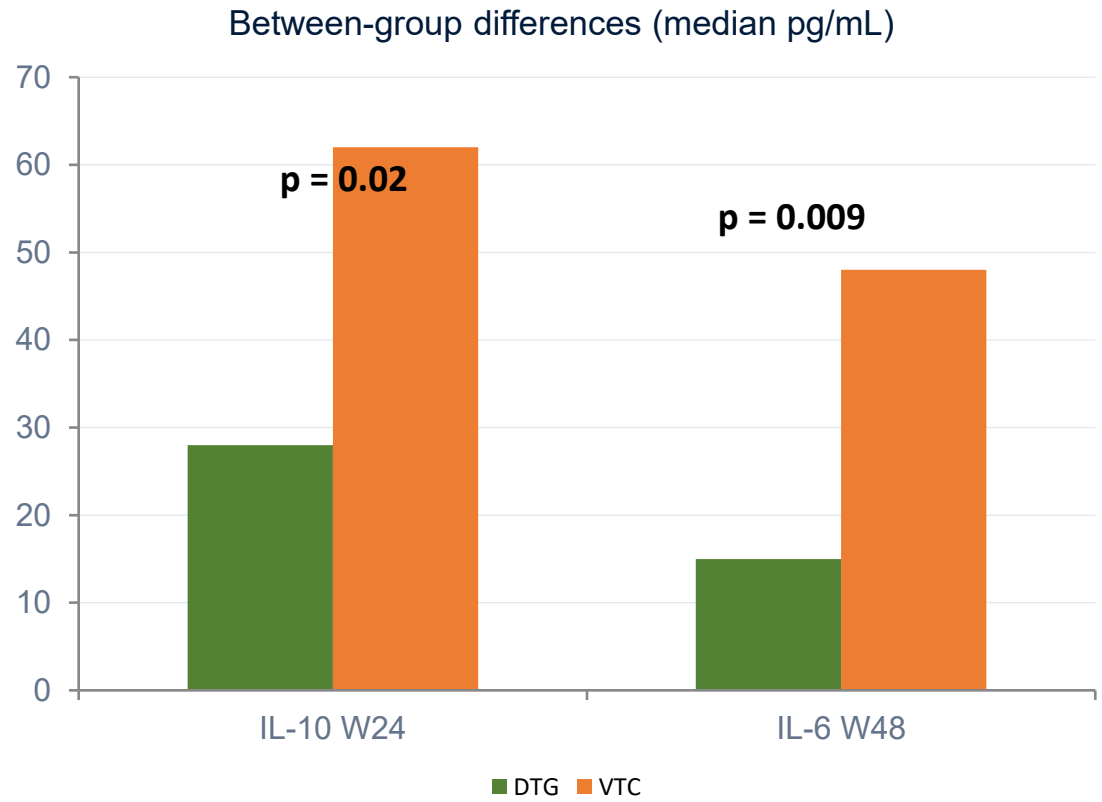
Results



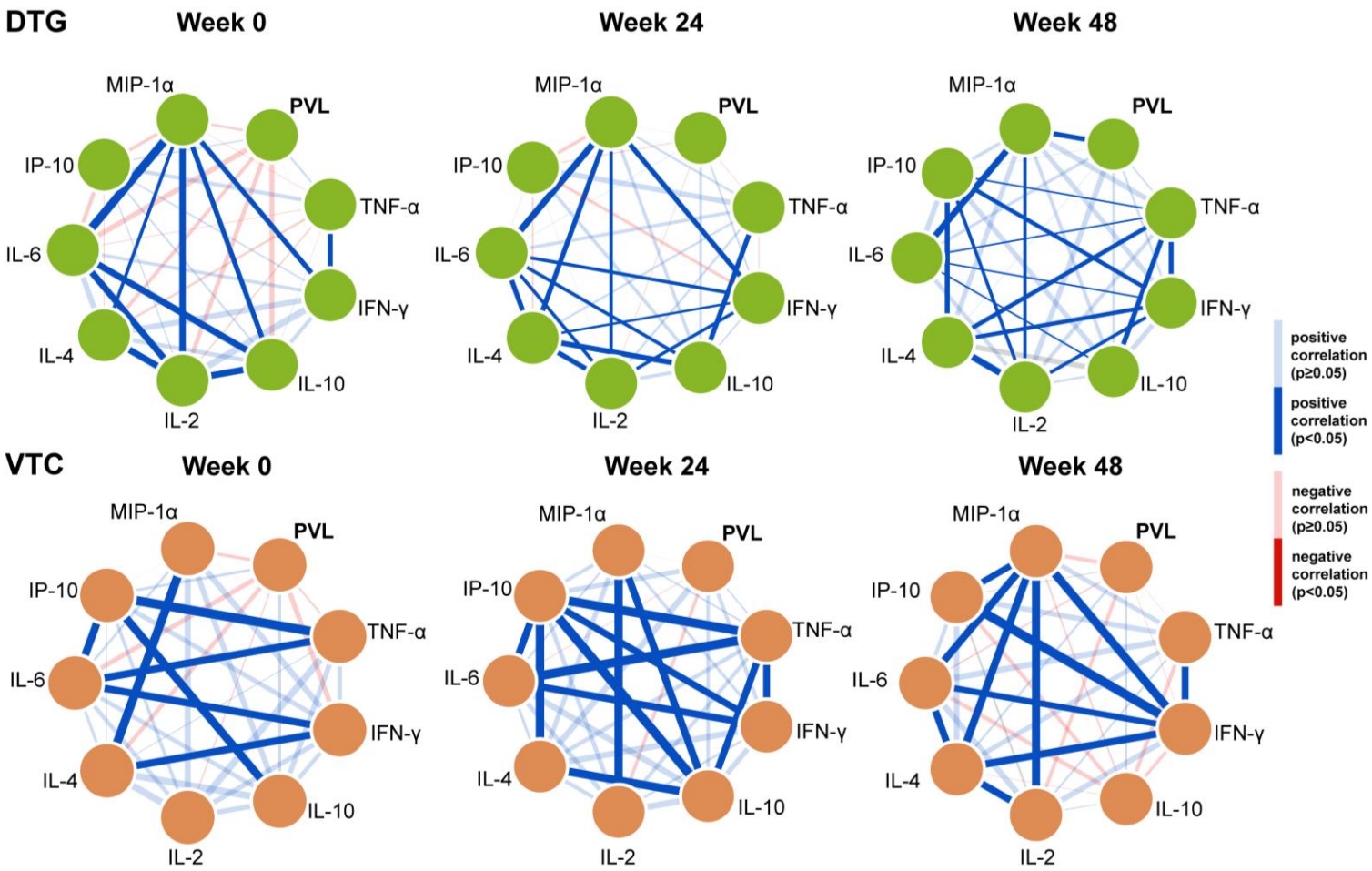
Scatter plots represent cytokine levels in the DTG (*A*) and VTC (*B*) groups. The red lines represent the median and the black lines represent the interquartile range. *$P < .05$

Significant Cytokine Changes





Cytokine Network Reorganization



Network analysis of the biomarker correlation matrices of cytokine levels and proviral load

Cytokine Levels: Key Findings

DTG Group

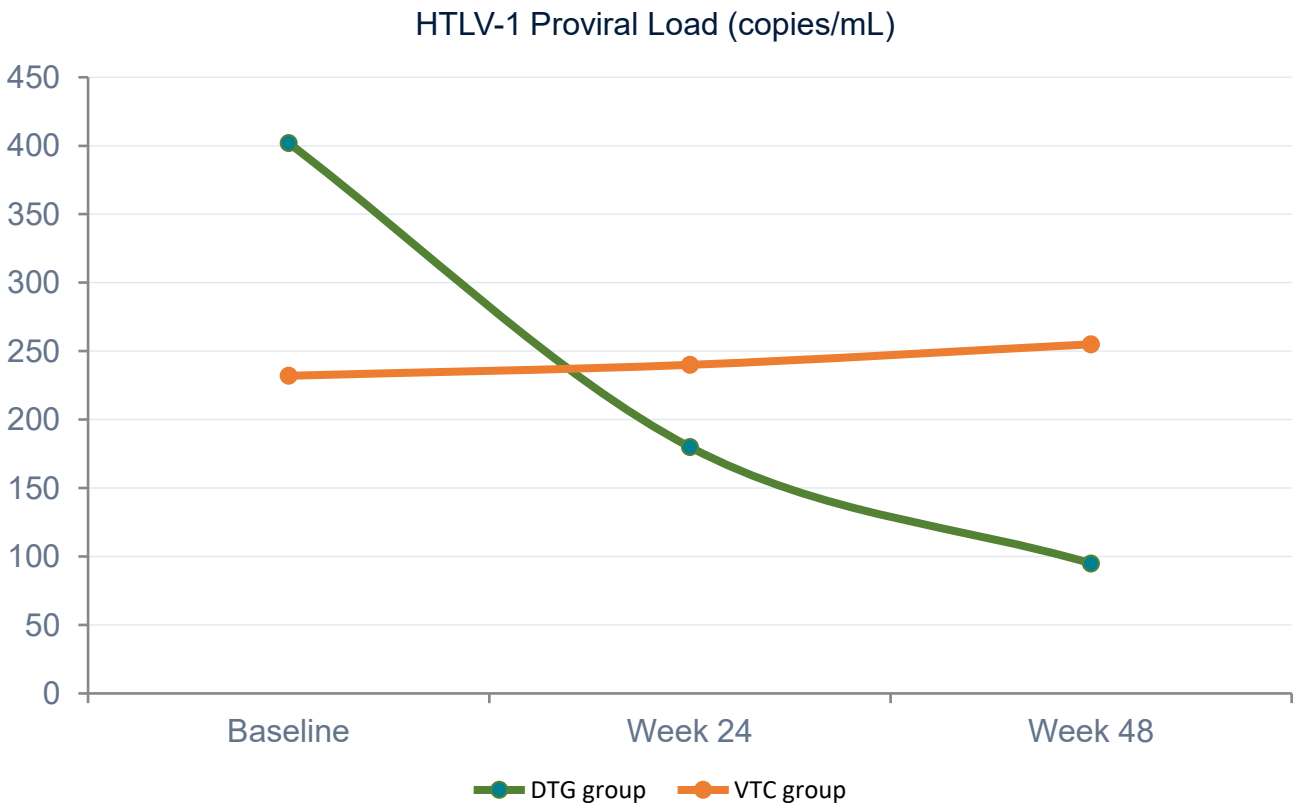
- Decrease in 7 of 8 cytokines at week 48 (all except TNF-α)
- IL-10 significantly lower vs VTC at week 24 (p = 0.02)
- IL-6 significantly lower vs VTC at week 48 (p = 0.009)
- IP-10 showed significant decrease within DTG group
- Loss of negative cytokine correlations → more balanced network

Vitamin C Group

- Increase in all 8 cytokine levels at week 48
- Persistent cytokine network dysregulation throughout
- No significant within-group changes in individual cytokines
- Maintained two-axis network pattern (IFN-γ and MIP-1α poles)
- Network pattern consistent with viral persistence

Key between-group differences: IL-10 at W24 (p=0.02) and IL-6 at W48 (p=0.009) were significantly lower in DTG vs VTC

PVL Reduction and Immune Modulation



DTG: Dual antiviral + immunomodulatory effect

- Significant PVL reduction at W24 and W48 ($p<0.001$ vs VTC)
- PVL positively correlated with MIP-1α and IL-6 in DTG group
- Participants with greatest PVL decrease showed most cytokine improvement
- Suggests active viral replication drives immune dysregulation in HTLV-1

Key insight: DTG use was associated with a significant and sustained decrease in PVL, accompanied by a shift toward a more balanced cytokine network — consistent with reduced viral-driven immune activation.

Conclusions

1. DTG use was associated with a decrease in plasma levels of 7 of 8 cytokines/chemokines tested at week 48, in contrast to an increase observed in the VTC group.

2. IL-10 (week 24) and IL-6 (week 48) were significantly lower in the DTG group compared to VTC — both markers linked to HTLV-1 persistence and Tax expression.

3. IP-10 showed a significant within-group decrease in the DTG arm, suggesting reduced interferon-driven inflammatory signaling.

4. DTG treatment reorganized the cytokine network from a dysregulated pattern (with negative correlations) to a more balanced profile, while VTC maintained immune dysregulation.

5. These findings support a dual antiviral and immunomodulatory role for dolutegravir in HTLV-1 infection and provide a rationale for larger trials.

Thank You

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