Updates on T-cell lymphomas

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Updates in Cancer Therapies | A Review of the 2023 ASCO & ESMO Annual Meetings | December 1-2, 2023

Overview

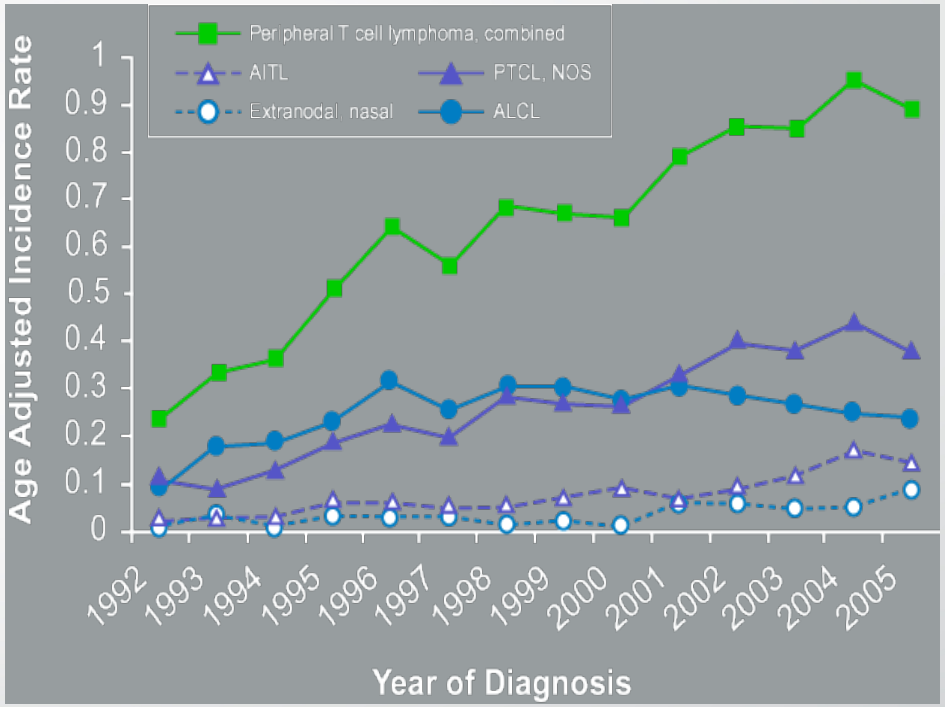
- This presentation will focus on a review of peripheral T-cell lymphoma (PTCL), which refers to mature (post-thymic) T-cell malignancies as supposed to immature (pre-thymic) T-cell lymphoblastic leukemia/lymphoma

- Recent updates in PTCL relate to advances made in phenotypic and molecular characterization of disease subtypes, combining biological agents, and development of cell-based therapies

- HTLV-1 related ATLL, a disease with dismal prognosis, and preliminary results from an ongoing U.S. trial (Miami) will also be discussed

PTCL

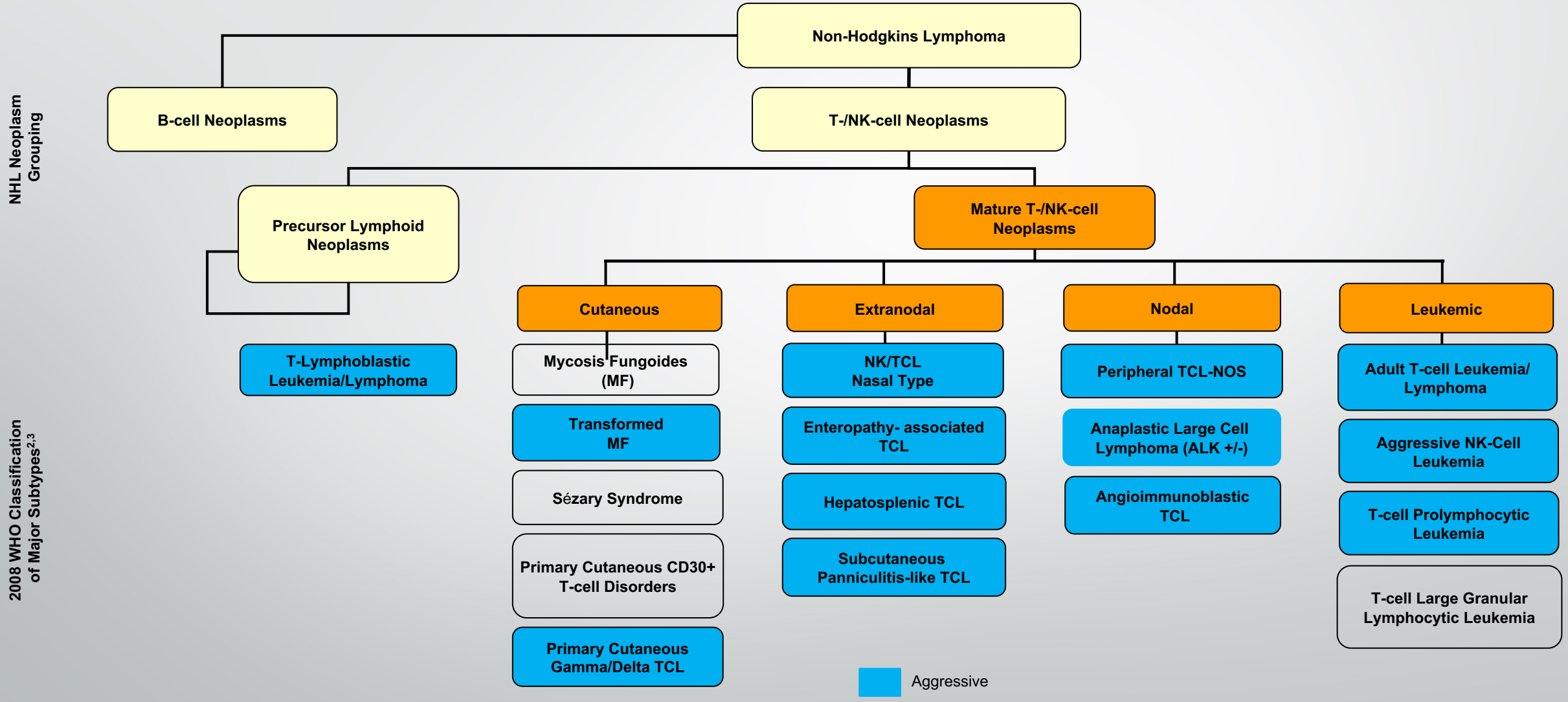
- A heterogenous disease of both aggressive and indolent disease with a growing number of subtypes being characterized recently
- 10–15% of new NHL cases per year[1]
- Appears to be increasing in incidence, in part due to an aging population [2,3]
- Most patients die of their disease and need stem cell transplant for possibility of cure



Reproduced from : Abouyabis AN, et al. *Leuk Lymphoma.* 2008;49:2099–2107.

1. O'Leary, HM, Savage KJ. *Curr Oncol Rep*. 2008;10:404–411.
2. Abouyabis AN, et al. *Leuk Lymphpoma.* 2008:49:2099–2107.
3. Morton LM, et al. *Blood*. 2006;107:265–276.

T-cell Lymphoma WHO Classification: 2008



1. Armitage JO, et al. *Ann Oncol.* 2004;15:1447–1449.
2. Adapted from Rodriguez J, et al. *Crit Rev Oncol Hematol*. 2008.
3. Adapted from Swerdlow SH, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 2008.

T-cell Lymphoma WHO Classification: 4th edition 2016

26 disease entities

CTCL	Extranodal	Nodal	Leukemic
Mycosis fungoides	NK/TCL Nasal Type	Peripheral TCL, NOS	Adult T-cell leukemia/lymphoma
Sezary syndrome	Enteropathy-associated T-cell lymphoma	Anaplastic large cell lymphoma, ALK+	Aggressive NK-cell leukemia
Primary cutaneous CD30+ T-cell disorders	Hepatosplenic TCL	Angioimmunoblastic TCL	T-cell prolymphocytic leukemia
Primary cutaneous gamma/delta TCL	Subcutaneous panniculitis-like TCL	Anaplastic large cell lymphoma, ALK-	T-cell large granular lymphocytic leukemia
Hydroa vacciniforme-like lymphoproliferative disorder	Monomorphic epitheliotropic intestinal T-cell lymphoma	Follicular TCL	Chronic lymphoproliferative disorder of NK-cells
Primary cutaneous CD8+ aggressive epidermotropic TCL	Systemic EBV+ T-cell lymphoma of childhood	Nodal peripheral TCL with TFH phenotype	
Primary cutaneous acral CD8+ T-cell lymphoma	Indolent T-cell lymphoproliferative disorder of the GI tract		
Primary cutaneous CD4+ small/medium T-cell lymphoma			

T-cell Lymphoma Classification: 5th edition 2022

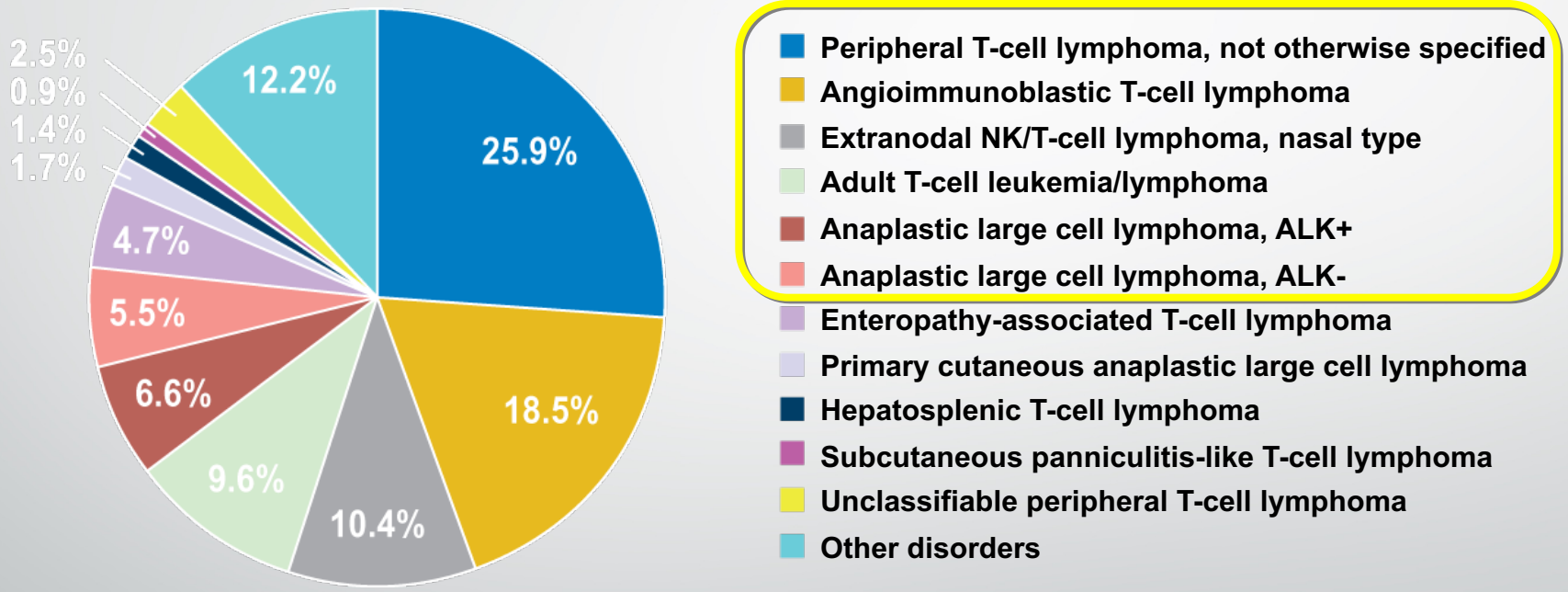
40 recognized disease entities (6 new ones since 4th edition)

WHO Classification, 5th edition	WHO Classification, revised 4th edition
Tumour-like lesions with T-cell predominance	
Kikuchi-Fujimoto disease	*Not previously included*
Indolent T-lymphoblastic proliferation	*Not previously included*
Autoimmune lymphoproliferative syndrome	*Not previously included*
Precursor T-cell neoplasms	
T-lymphoblastic leukaemia/lymphoma	
T-lymphoblastic leukaemia / lymphoma, NOS	T-lymphoblastic leukaemia/lymphoma
Early T-precursor lymphoblastic leukaemia / lymphoma	Early T-cell precursor lymphoblastic leukaemia
(Entity deleted)	NK-lymphoblastic leukaemia/lymphoma
Mature T-cell and NK-cell neoplasms	
Mature T-cell and NK-cell leukaemias	
T-prolymphocytic leukaemia	(Same)
T-large granular lymphocytic leukaemia	T-cell large granular lymphocytic leukaemia
NK-large granular lymphocytic leukaemia	Chronic lymphoproliferative disorder of NK cells
Adult T-cell leukaemia/lymphoma	(Same)
Sezary syndrome	(Same)
Aggressive NK-cell leukaemia	(Same)
Primary cutaneous T-cell lymphomas	
Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder	(Same)
Primary cutaneous acral CD8-positive lymphoproliferative disorder	Primary cutaneous acral CD8-positive T-cell lymphoma
Mycosis fungoides	(Same)
Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: Lymphomatoid papulosis	(Same)
Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: Primary cutaneous anaplastic large cell lymphoma	(Same)
Subcutaneous panniculitis-like T-cell lymphoma	(Same)
Primary cutaneous gamma/delta T-cell lymphoma	(Same)
Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma	(Same)
Primary cutaneous peripheral T-cell lymphoma, NOS	*Not previously included*
Intestinal T-cell and NK-cell lymphoid proliferations and lymphomas	
Indolent T-cell lymphoma of the gastrointestinal tract	Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract
Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract	*Not previously included*
Enteropathy-associated T-cell lymphoma	(Same)
Monomorphic epitheliotropic intestinal T-cell lymphoma	(Same)
Intestinal T-cell lymphoma, NOS	(Same)
Hepatosplenic T-cell lymphoma	
Hepatosplenic T-cell lymphoma	(Same)
Anaplastic large cell lymphoma	
ALK-positive anaplastic large cell lymphoma	Anaplastic large cell lymphoma, ALK-positive
ALK-negative anaplastic large cell lymphoma	Anaplastic large cell lymphoma, ALK-negative
Breast implant-associated anaplastic large cell lymphoma	(Same)
Nodal T-follicular helper (TFH) cell lymphoma	
Nodal TFH cell lymphoma, angioimmunoblastic-type	Angioimmunoblastic T-cell lymphoma
Nodal TFH cell lymphoma, follicular-type	Follicular T-cell lymphoma
Nodal TFH cell lymphoma, NOS	Nodal peripheral T-cell lymphoma with TFH phenotype
Other peripheral T-cell lymphomas	
Peripheral T-cell lymphoma, not otherwise specified	(Same)
EBV-positive NK/T-cell lymphomas	
EBV-positive nodal T- and NK-cell lymphoma	*Not previously included*
Extranodal NK/T-cell lymphoma	Extranodal NK/T-cell lymphoma, nasal-type
EBV-positive T- and NK-cell lymphoid proliferations and lymphomas of childhood	
Severe mosquito bite allergy	(Same)
Hydroa vacciniforme lymphoproliferative disorder	Hydroa vacciniforme-like lymphoproliferative disorder
Systemic chronic active EBV disease	Chronic active EBV infection of T- and NK-cell type, systemic form
Systemic EBV-positive T-cell lymphoma of childhood	(Same)

Allagio et al. *Leukemia* 2022

Relative Frequency of PTCL Subtypes

- PTCL-NOS is the most common subtype



Armitage J, et al. *J Clin Oncol.* 2008;26:4124–4130.

Intestinal T-cell and NK-cell lymphoid proliferations and lymphomas: Pathophysiology

Indolent T-cell lymphoma of the gastrointestinal tract
Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma
Intestinal T-cell lymphoma, NOS

- **Indolent T-cell lymphoma of the gastrointestinal (GI) tract:** Alterations in JAK-STAT pathway genes, mutations in epigenetic genes (e.g., *TET2*, *KMT2D*), *STAT3*::*JAK2* fusions, structural alterations involving the *IL2* gene

- **Indolent NK-cell lymphoproliferative disorder of the GI tract** (iNKLPD): *JAK3* mutations

Anaplastic large cell lymphoma (ALCL): Pathophysiology

ALK-positive anaplastic large cell lymphoma
ALK-negative anaplastic large cell lymphoma
Breast implant-associated anaplastic large cell lymphoma

- **ALK positive anaplastic large cell lymphoma (ALK+ ALCL):** t(2;5): NPM-ALK fusion in 60%, IRF4/MUM-1+ in >90%

- **ALK negative ALCL (ALK- ALCL):** *P63* rearrangements, loss of *TP53*, overexpression of IL-2Rα, *DUSP22* rearrangement, aberrant ERBB4 protein expression, JAK2 rearrangements

- **Breast implant-associated ALCL (BIA-ALCL):** 9p24.1, overexpression of PD-L1 in over 50% , constitutive JAK-STAT activation by somatic mutations of *STAT3, STAT5B, JAK1 and JAK2* and loss-of function mutations of *SOCS1* and *SOCS3*

Mature T-cell and NK-cell leukemias: Pathophysiology

- **T-prolymphocytic leukemia (T-PLL)**: Breakpoints affecting *TCL1A* or *MTCP1* loci, TCL1 expression. Abnormalities involving chromosome 11 (11q22.3; ATM), chromosome 8: idic(8)(p11), t(8;8), trisomy 8q, chromosomes 5, 12, 13, 22, or complex karyotype

- **T-large granular lymphocytic leukemia (T-LGLL):** STAT3 and STAT5B mutations. Cytogenetics (FISH and karyotype): inv(14)(q11;q32); t(14;14)(q11;q32); t(X;14)(q28;q11); trisomy 8

- **Adult T-cell leukemia/lymphoma (ATLL):** HTLV-1 in 100%
  - Mutations affecting TCR-NF-κB signaling, CTLA4 CD28 and ICOS, CD28 fusions, REL C-terminal truncations, recurrent alterations in HLA-A and HLA-B, structural variations disrupting the 3'-untranslated region of CD274 (PD-L1)
  - *STAT3* mutations are more common in indolent

- **Aggressive NK-cell leukemia (ANKL):** JAK/STAT and RAS/MAPK pathways genes, epigenetic modifiers (TET2, CREBBP, KMT2D), and immune checkpoint molecules CD274 (PD-L1)/PDCD1LG2 (PD-L2)

Nodal T-follicular helper cell lymphomas: Pathophysiology

Nodal TFH cell lymphoma, angioimmunoblastic-type
Nodal TFH cell lymphoma, follicular-type
Nodal TFH cell lymphoma, NOS

- **Nodal T-follicular helper cell lymphoma, angioimmunoblastic-type (**nTFHL-AI**):** Mutations commonly affecting epigenetic genes: *TET2*, *DNMT3A*, *RHOA*, and *IDH2*

- **Nodal TFH-cell lymphoma, follicular-type** (nTFHL-F) and **Nodal TFH-cell lymphoma, not otherwise:** Overlap with THF markers above in addition to PD1, ICOS, CXCL13, CD10, and BCL6 mutations

Other peripheral T-cell and NK-cell lymphomas:

- **Peripheral T-cell lymphoma NOS (PTCL-NOS):** A heterogeneous category of "garden variety" and a diagnosis of exclusion

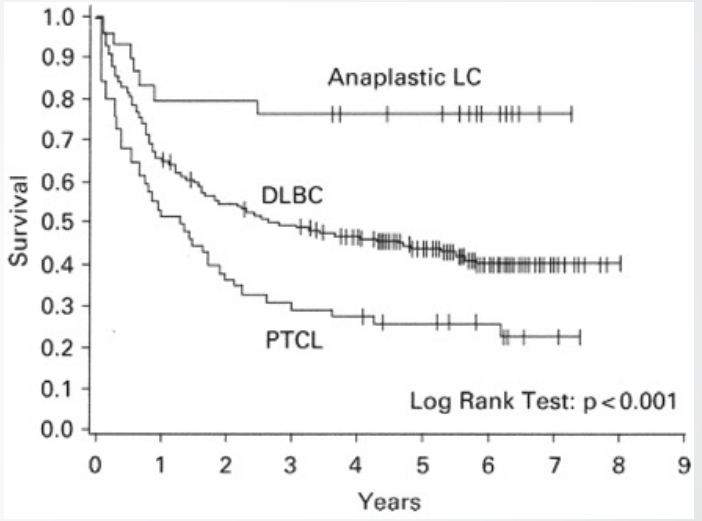
- **Hepatosplenic T-cell lymphoma:** TCRγ gene rearrangement to reflect clonality. Activating mutations of JAK/STAT pathway (i.e., STAT5B, STAT3), and chromatin-modifying genes (i.e., SETD2, INO80, ARID1B). Cytogenetics: isochromosome 7q, trisomy 8.

- **EBV-positive nodal T- and NK-cell lymphoma:** EBV+ 100% (EBER-ISH)

Prognosis of PTCL

Most subtypes have a worse prognosis than aggressive B-cell NHL

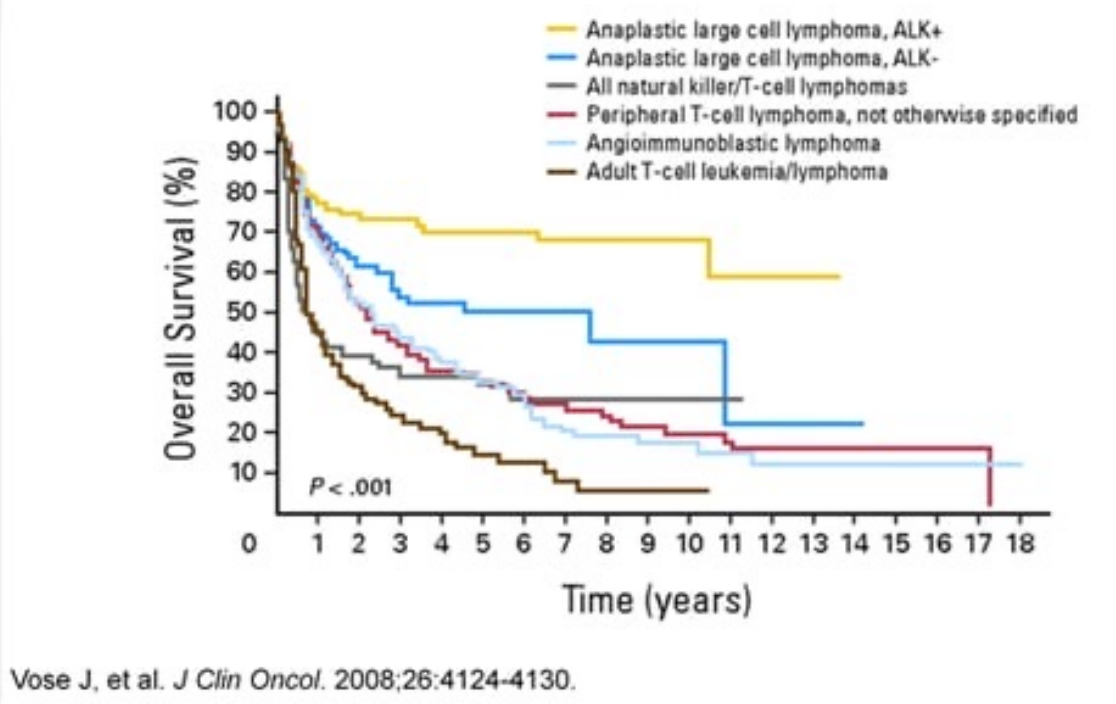
- Median overall survival is 1–3 yrs[1,2]
- 5-yr overall survival ~26%[3]
- ALK+ ALCL has a favorable outcome: 5-yr survival of 65–90%[2]



1. Armitage JO, et al. *Ann Oncol.* 2004;15:1447–1449.
2. Savage KJ. *Blood Rev.* 2007;21:201–216.
3. Rüdiger T, et al. *Ann Oncol.* 2002;13:140–149.

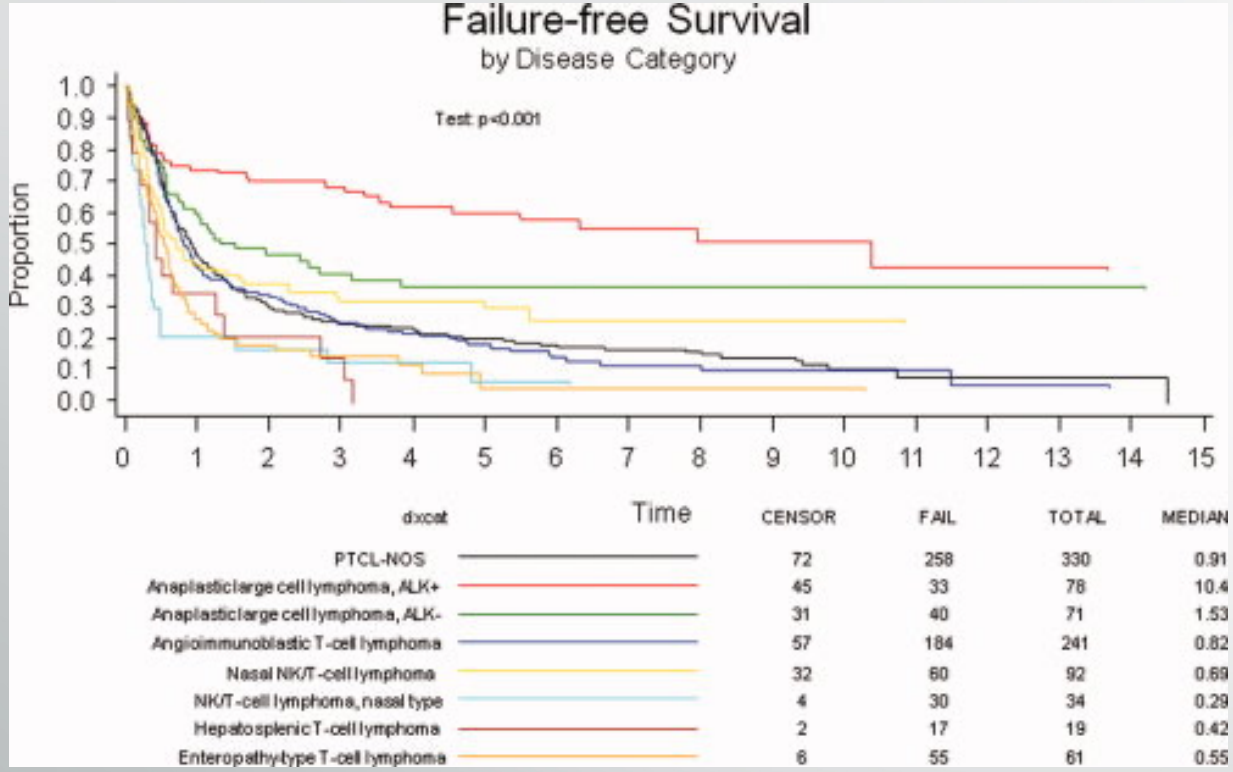
Survival times less than 1 year:

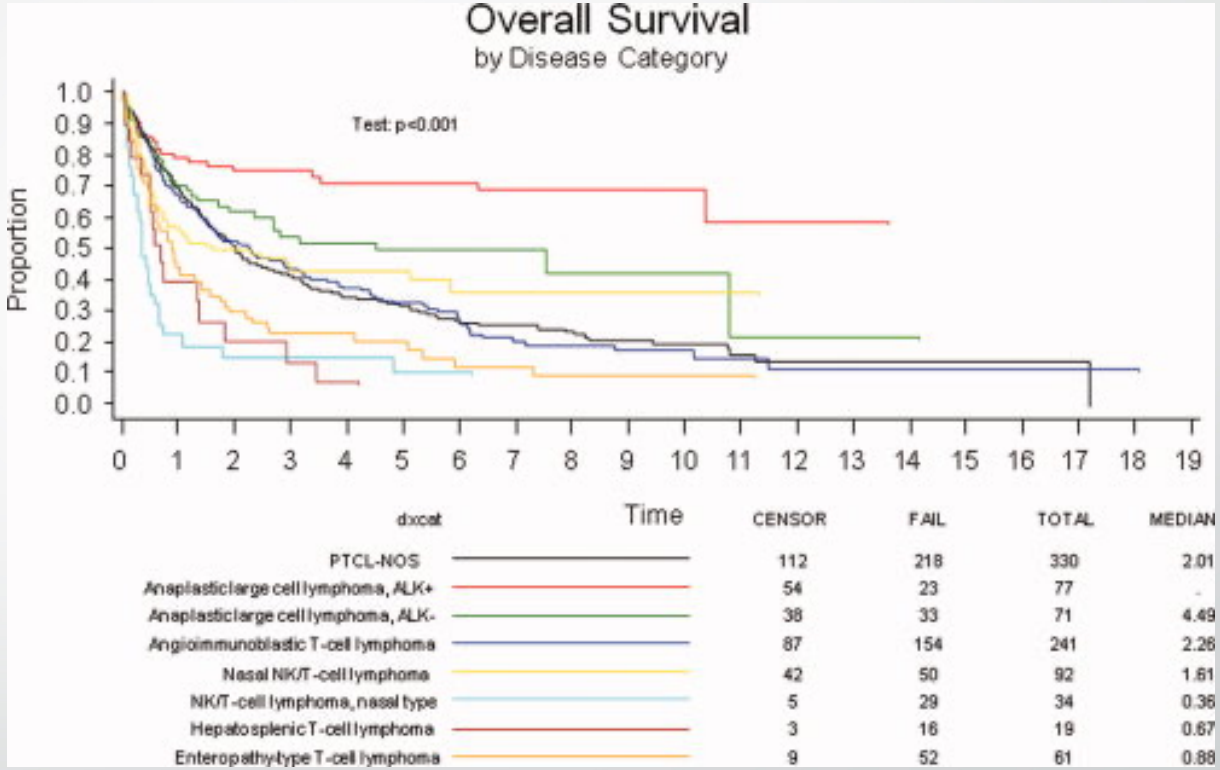
- Hepatosplenic TCL
- ATLL (acute and lymphomatous)
- Primary cutaneous gamma/delta TCL
- Aggressive NK-cell leukemia
- Enteropathy associated TCL
- Monomorphic epitheliotropic intestinal TCL



Vose J, et al. *J Clin Oncol.* 2008;26:4124-4130.

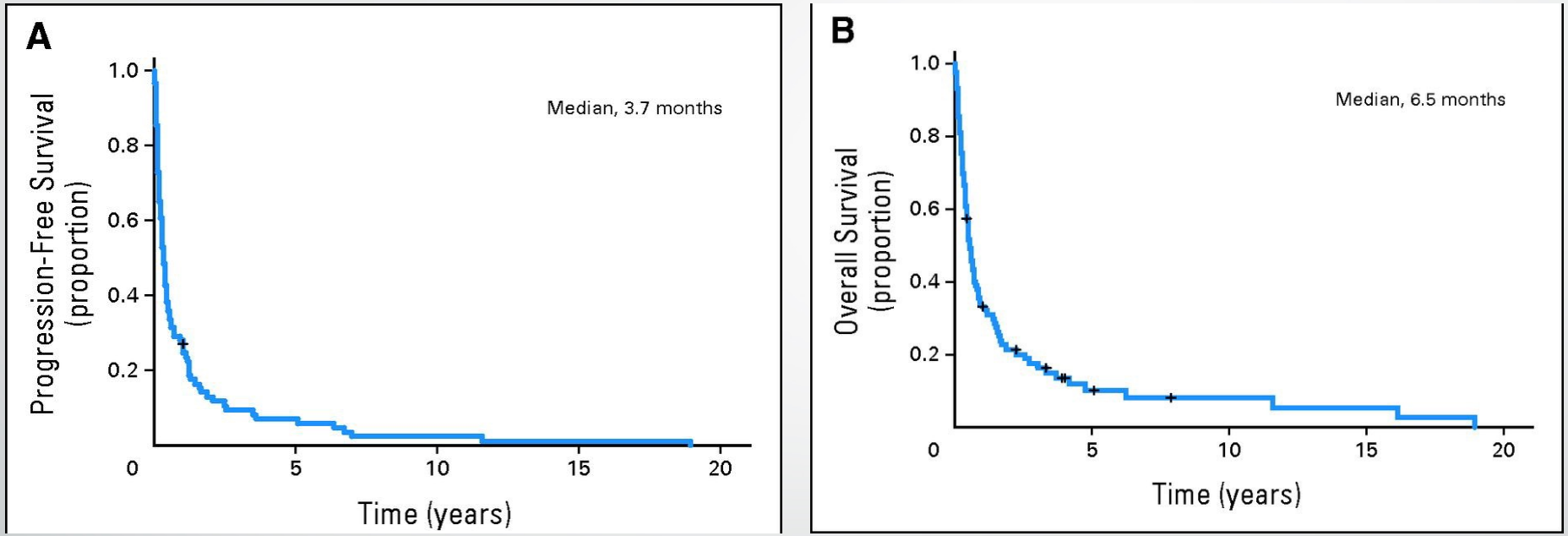
Aggressive PTCL: 2012 Update on Prognosis





Armitage
American Journal of Hematology
Volume 87, Issue 5, pages 511-519, 17 APR 2012

PTCL Survival After First Relapse



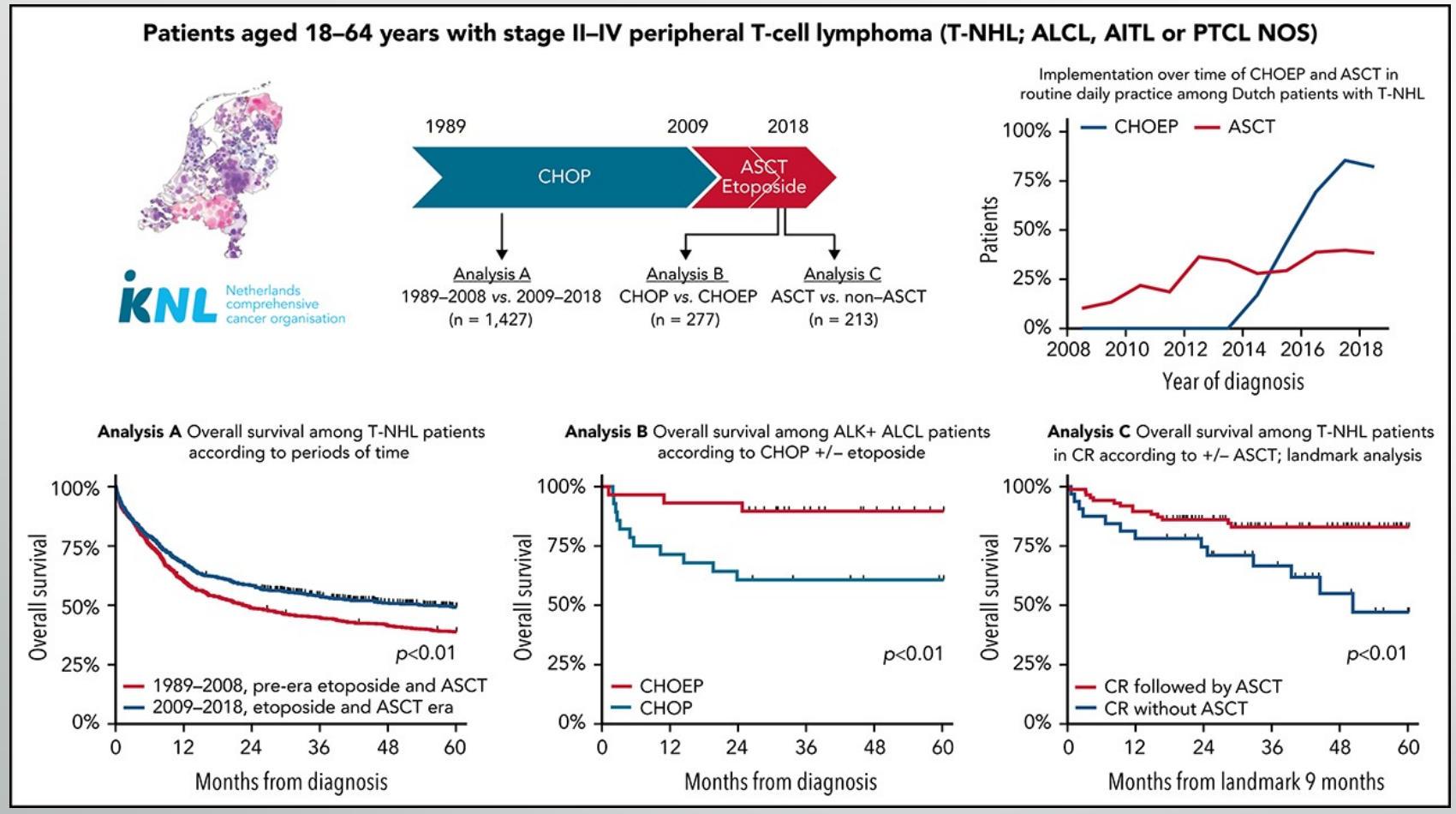
Mak *et al JCO* 2013

Treatment Options for PTCL

- **PTCL-NOS, ALK- ALCL , AITL; EATL; MEITL; nodal TFH:**
  - **For transplant candidates:** CHP + brentuximab if CD30+, CHOP, CHOEP, DA-EPOCH, HyperCVAD, CHOP followed by IVE (for EATL)
  - **Non-transplant candidates:** brentuximab for CD30+ HDAC inhibitors (belinostat or romidepsin, preferred also for AITL and nodal TFH), pralatrexate. Other drugs: alemtuzumab, bendamustine, bortezomib, cyclophosphamide and/or etoposide, duvelisib, gemcitabine, lenalidomide, ruxolitinib
  - **For relapse:** Salvage regimens (DHA + platinum ,GDP, GEMOX, , GVD, ICE), or above non-transplant candidate regimens
- **Hepatosplenic T-cell lymphoma:** ICE followed by transplant (allogeneic ideally); CHOEP, DA-EPOCH, DHA + platinum, HyperCVAD, IVAC
- **NK-T-cell lymphomas:** Asparaginase-based regimens: *Modified SMILE, P-GEMOX , DDGP, AspaMetDex.* **For localized disease *DeVIC (or SMILE or P-GEMOX)* + XRT !!!**
- **ALK+ ALCL positive:** CHP + brentuximab. For relapsed: use above second line/non-transplant candidate agents, **alectinib, or crizotinib**
- **Breast implant-associated ALCL**: Remove implant; brentuximab or combination chemo beyond localized disease
- **T-cell LGL:** if treatment indicated: low-dose methotrexate ±corticosteroids, oral cyclophosphamide ± corticosteroids, cyclosporine ±corticosteroids
- **T-prolymphocytic leukemia (T-PLL**): alemtuzumab, pentostatin (single agent or combined)

For relapse: pembrolizumab, nivolumab

Autologous HCT



Consider auto HCT in:

- Patient younger than 60
- Have an advanced-stage TCL
- Relapsed after first-line therapy

Schmitz N, et al. Blood. 2010

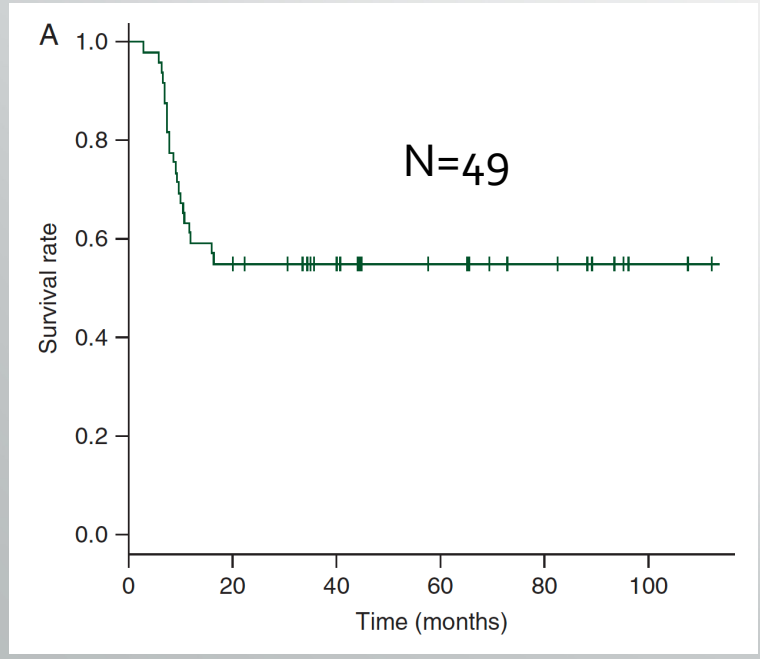
Allogeneic HCT

Annals of Oncology 26: 386–392, 2015
doi:10.1093/annonc/mdu515
Published online 12 November 2014

Upfront allogeneic stem-cell transplantation for patients with nonlocalized untreated peripheral T-cell lymphoma: an intention-to-treat analysis from a single center

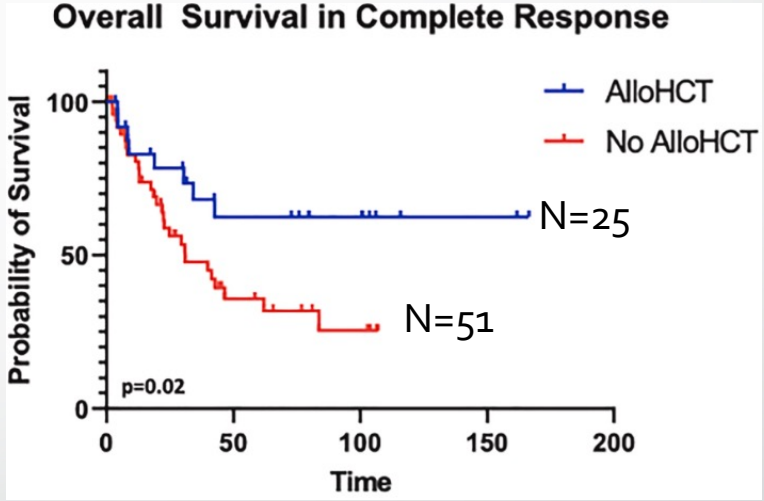
M. Loirat[1], P. Chevallier[1], C. Leux[2], A. Moreau[3], C. Bossard[3], T. Guillaume[1], T. Gastinne[1], J. Delaunay[1], N. Blin[1], B. Mahé[1], V. Dubruille[1], K. Augeul-Meunier[1], P. Peterlin[1], H. Maisonneuve[4], P. Moreau[5], N. Juge-Morineau[6], H. Jardel[7], M. Mohty[8], P. Moreau[1] & S. Le Gouill[1,9,10]*

Departments of [1]Hematology; [2]Epidemiology; [3]Pathology, University Hospital of Nantes, Nantes; [4]Department of Hematology, CHD de la Roche-Sur-Yon; [5]Department of Hematology, CH de Lorient, La Roche-Sur-Yon; [6]Department of Hematology, Centre Catherine de Sienne, Rezé; [7]Department of Hematology, CH de Vannes, Vannes; [8]Department of Hematology, Saint-antoine, APHP, Paris; [9]INSERM, UMR892, Equipe 10, Nantes; [10]INSERM, CIC 004, Nantes University Hospital, Nantes, France



Outcomes for Patients with Relapsed and Refractory Peripheral T-Cell Lymphoma in the 21st Century By Relapse Status, Salvage Therapy, and Receipt of Allogeneic Transplant (Horwitz et al. ASH 2022)

Salvage after 1st remission



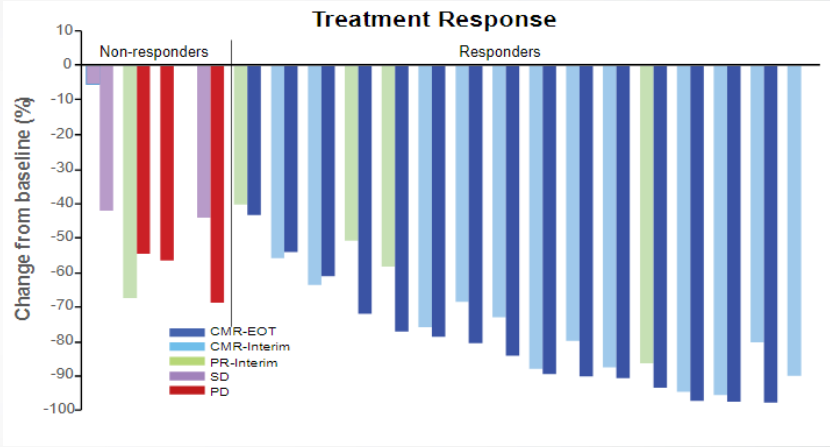
- No randomized data
- Toxicity/mortality may outweigh upfront auto HCT
- Consider upfront allo-HCT in:
  - ATLL
  - Hepatosplenic TCL
  - Enteropathy-associated TCL
  - Advanced CTCL

Recently Published and Ongoing Clinical Trials for PTCL

Multicenter, Phase II study of CC486-CHOP in patients with previously untreated PTCL (Ruan et al, Blood. 2023)

N=20, CR 75% (88.2% on PTCL-TFH)
2-y PFS 65.8% (69.2% PTCL-TFH)
2-yr OS 68.4% (76.1% PTCL-TFH)

5-aza-CHOP induced a sustained response in pts with AITL / TFH
TET2 mutations: associated with CR (p=0.007), favorable PFS (p=0.004) and OS(p=0.015)
DNMT3A mutations: associated with adverse PFS (p=0.016)



Romidepsin Plus CHOP Versus CHOP in Patients With Previously Untreated Peripheral T-Cell Lymphoma: Results of the Ro-CHOP Phase III Study [Bachy et al. J Clin Oncol. 2022 Jan 20;40(3)]. **Romidepsin + CHOP did not improve OS or PFS!**

<u>Important ongoing trials:</u>

Alliance A059102: A randomized phase II U.S. intergroup study of CHO(E)P versus CC-486-CHO(E)P versus duvelisib-CHO(E)P in previously untreated, CD30-negative, peripheral T-cell lymphomas (Mehta-Shah et al)

Phase I Multicenter Study of Ruxolitinib and Duvelisib in Relapsed or Refractory T- or NK-Cell Lymphomas (IIT MSKCC)

Pilot study of pembrolizumab in untreated extranodal, NK/T cell lymphoma, nasal type (IIT MSKCC)

Other Emerging Therapies from Prospective Trials for PTCL

ASCO 2023

A phase 2 trial of CHOP with anti-CCR4 antibody mogamulizumab for elderly patients with CCR4-positive adult T-cell leukemia/lymphoma (Choi et al. J Clin Oncol 41, 2023 (suppl 16; abstr 7504). 48 pts, median age 74 years, ATL subtypes included 31, 9, and 8 patients for the 31 acute, 9 lymphoma, and 8 unfavorable chronic type, 1-year PFS was 36.2% median 0.7 years), and ORR 91.7% (CR 64.6%). 1-yr OS 66.0% and median OS 1.6 years. The most frequent AEs grades 3/4, were lymphocytopenia (97.9%), neutropenia (89.6%), febrile neutropenia (64.8%), anemia (58.3%), thrombocytopenia (45.8%)

Golidocitinib (oral JAK1-selective inhibitor) in treating refractory or relapsed peripheral T-cell lymphoma: Primary analysis of the multinational pivotal study results (JACKPOT8) (Cai et al. J Clin Oncol 41, 2023 suppl 16; abstr 7503). 80 pts: AITL (56.3%), NOS (45.7%), ALCL (11.1%) and others (44.4%). Well tolerated. The median prior lines = 2. ORR = 43.8% (CR 25.0%). The longest DOR was 15.7 months (still responding).

Systemic VSV-IFNβ-NIS oncolytic virotherapy in patients with relapsed refractory T-cell lymphoma (Bennani et al. 10.1200/JCO.2023.41.16_suppl.7530) 11 pts (mycosis fungoides N=3; ALK- ALCL N=1; PTCL-NOS N=2; AITL N=4; Nodal TFH N=2). Median of 3 lines of therapy. Well tolerated, grade 1-2 CRS in 81%, were short lasting and attributed to IFN-B toxicity. For PTCL (N=9), there were 5 responses (3CR) with two long-lasting at 24 months. Expansion cohort of 20 PTCL will be added.

Other Emerging Therapies from Prospective Trials for PTCL

ASCO 2023

EZH2/EZH1 inhibitor tulmimetostat (CPI-0209) in patients with advanced solid tumors or hematologic malignancies: Preliminary phase II results (Drescher et al, J Clin Oncol 41, 2023 (suppl 16; abstr 3094). 2 CR and 1 PR in 7 pts with PTCL

A phase 1a/b study of BR101801, a PI3K γ/δ and DNA PK triple inhibitor, in adult patients with advanced hematologic malignancies (NCT04018248) (Kim et al. 10.1200/JCO.2023.41.16_suppl.7551). Of 7 evaluable patients with PTCL (PTCL-NOS and AITL), ORR was 42.9%. Goal is to enroll 12 pts.

Synergistic anti-tumor activity of the mTOR inhibitor everolimus and gemcitabine for the treatment of peripheral T cell lymphoma (Huang et al. 10.1200/JCO.2023.41.16_suppl.e19538) 24 R/R PTCL patients, ORR of 70.8%, 45.8% CR, median DOR 16.8 months, median PFS 9.9 months. Functional in vitro studies showed synergistic inhibition of cell viability and apoptosis in PTCL cell lines. Transcriptomic profiling indicated that the synergistic effect was induced through the abrogation of MYC pathway.

Other Emerging Therapies from Prospective Trials for PTCL

ASH 2022

Updated Results of an Investigator-Initiated Phase II Study of Pembrolizumab and Romidepsin for Patients with Relapsed or Refractory T-Cell Lymphoma (TCL) with Survival Analysis [Yyer at al. *Blood* (2022) 140 (Supplement 1): 2313–2315). 28 pts, CR 34.2% (ORR of 39.5%), median PFS time 29.5 months

Oral Azacytidine in Patients with Relapsed/Refractory Angioimmunoblastic T-Cell Lymphoma: Final Analysis of the Oracle Phase III Study (Dupuis et al. *Blood* (2022) 140 (Supplement 1): 2310–2312). 86 pts randomized against investigator's choice (gemcitabine, n=24, bendamustine n=16, romidepsin n=4). Confirmed path AITL n=69), and TFH n=9 cases. Similar CR rates. Median PFS in the CC-486 arm was 5.6 vs 2.8 months (p=0.0421). OS 18.4 vs 10.3 months.

ITK Inhibitor Induces Dose-Dependent Th1 Skewing in Normal T Cells and Is Active in Refractory T Cell Lymphomas [Song et al. *Blood* (2022) 140 (Supplement 1)]. 33 pts: PTCL-NOS (17), AITL (4), and CTCL (12). Well tolerated. Response in evaluable pts (N=10) 1 CR 25 mo; 1 PR 2+ month ; 1 nodal CR 16 mo (CTCL); 2 SD; 1 PD.

Results from a Phase I Trial Using Nivolumab in Combination with Dose Adjusted EPOCH in Newly Diagnosed Peripheral T-Cell Lymphomas [Haverkos et al. *Blood* (2022) 140 (Supplement 1)]. 18 pts (11 CR, 5 PR). Exploratory analyses, including expression of PD-1 and PDL-1 is ongoing.

A Phase 2 Study of Pembrolizumab (MK-3475) after Autologous Stem Cell Transplantation in Patients with T-Cell Non-Hodgkin Lymphoma [Merrill et al. *Blood* (2022) 140 (Supplement 1)]. 21 pts: PTCL NOS (52%), AITL (19%), extranodal NK/T (14%), ALK- ALCL (10%) and monomorphic EITL (5%). 13 of 21 (62%) were progression-free at 18-months

Other Emerging Therapies from Prospective Trials for PTCL

ASH 2022

A Multicenter, Phase III Study of Chidamide, Azacitidine Combined with CHOP Versus CHOP in Patients with Untreated Peripheral T-Cell Lymphoma (ClinicalTrials.gov - NCT05075460) [(Wei et al. Blood (2022) 140 (Supplement 1)] **PTCL** NOS (n = 14) and AITL (n = 21). No difference in efficacy.

Pembrolizumab in Combination with Epigenetic Therapy Is Safe and Active in Heavily Treated Patients with Peripheral T-Cell Lymphoma (PTCL) and Cutaneous T-Cell Lymphoma (CTCL): Preliminary Results from the Embolden Trial [(Roberts et al. Blood (2022) 140 (Supplement 1)]**.** Pralatrexate alone (Arm A), pralatrexate + decitabine (Arm B), or decitabine alone (Arm C). 15 patients so far. DLTs in Arms A (n=1), B (n=2, grade 3 thrombocytopenia and febrile neutropenia), and C (n= 3, grade 3 hyponatremia and rash, grade 4 thrombocytopenia, neutropenia, and anemia). 9 /15 patients evaluable: 1 CR (Arm B), and 2 PR (Arm A, Arm B).

Preliminary Biomarker Data from a Phase 1/2 Study of Golidocitinib Demonstrates Targeting JAK/STAT Pathway to Treat Peripheral T-Cell Lymphoma (Song et al. https://doi.org/10.1182/blood-2022-162947)**.** 49 pts. Well tolerated. ORR 42.9% (CR 22.4%). In 20 pts with tissue there was a trend towers a better response in cases with high expression of pSTAT3.

Emerging Cell-based Therapies for PTCL

- Anti-CD70 allo CAR-T (Iyer et al. EHA 2022)

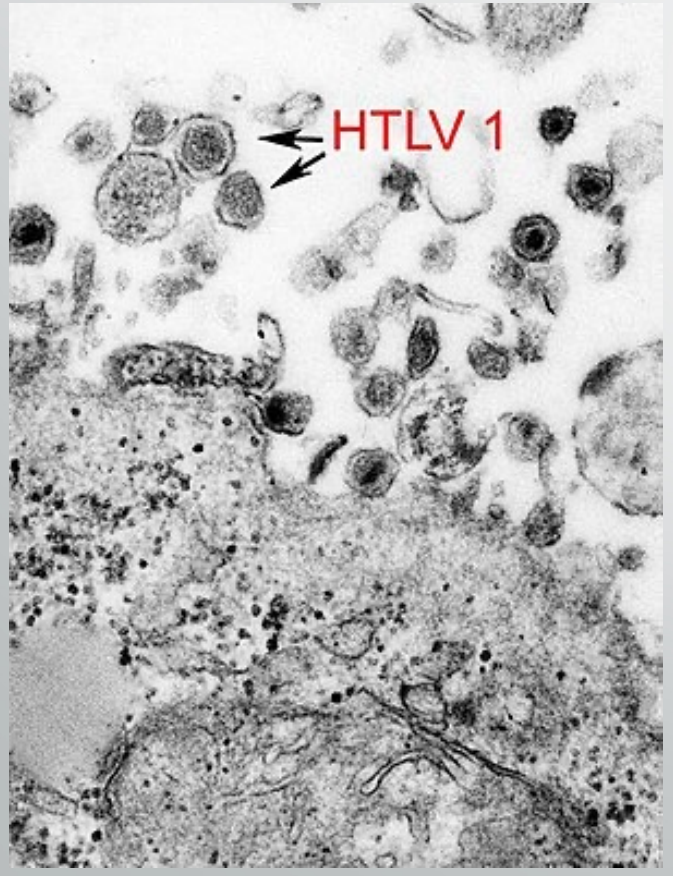
  COBALT-LYM STUDY OF CTX130: A PHASE DOSE ESCALATION STUDY OF CD70- TARGETED ALLOGENEIC CRISPR-CAS9–ENGINEERED CAR T CELLS IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) T-CELL MALIGNANCIES

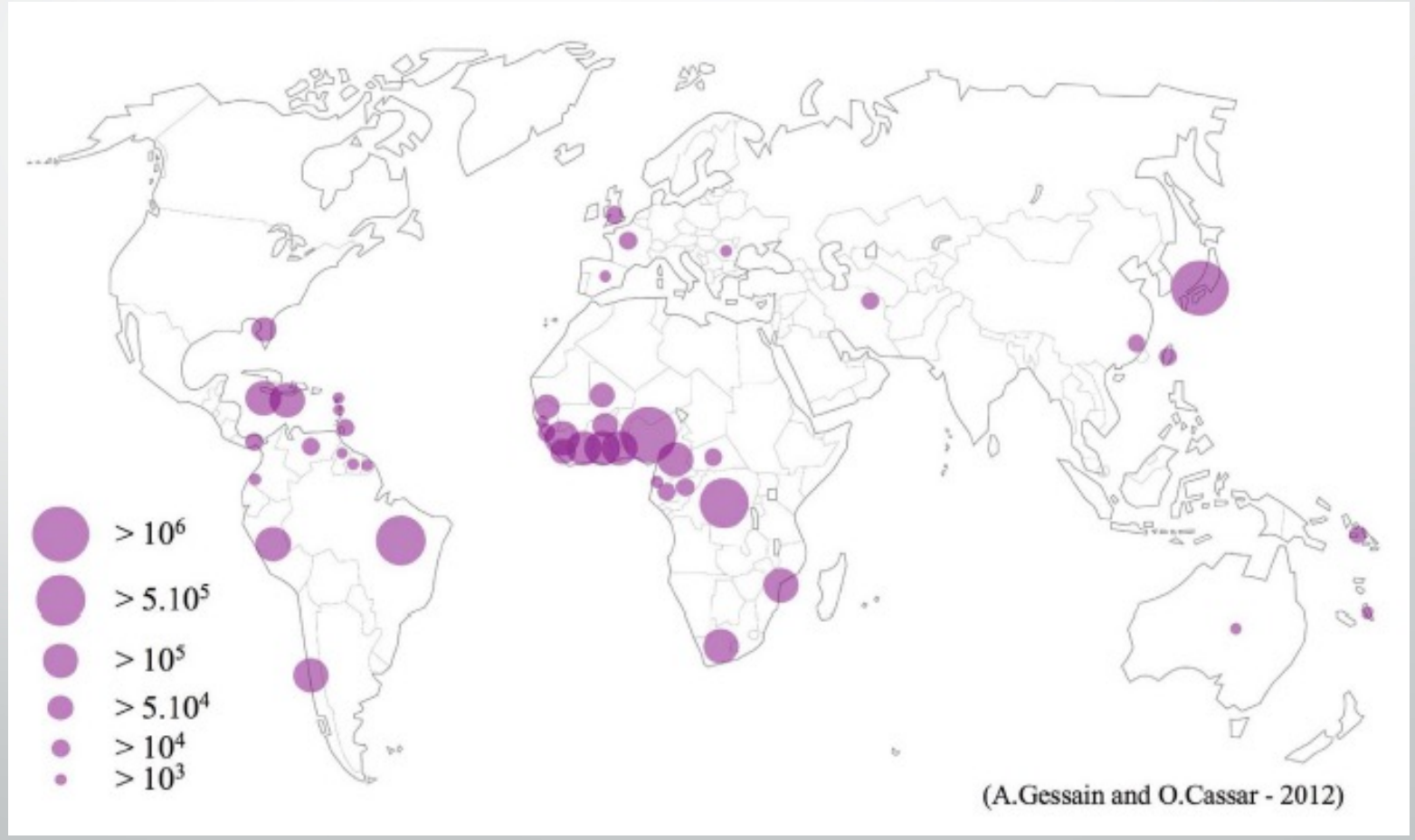
  n= 15, 7 PTCL and 8 CTCL, ORR 71%, (CR 29%)

- Anti-CD3 CAR-T cell (Qian et al, ASH, 2022)
- TRBC1-Targeting CAR T: AUTO4 (Cwynarski, ASH 2022)
- Anti-CD4 CAR-T cell (e.g., Sezary syndrome)
- CD30 CAR-T cell (e.g., EATL treated with CAR-T after allo-HCT [Voorhees, Blood Advances, 2020]).
- Anti-CD5 CAR-T cell (Hill, ASH, 2019)

Adult T-cell leukemia-lymphoma (ATLL)

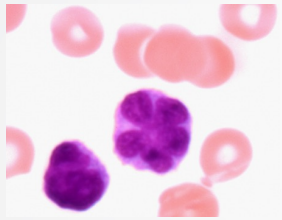
- An aggressive CD4+ peripheral T- cell malignancy caused by the human T-cell leukemia virus (HTLV-1)
- Frequently encountered in HTLV-1 endemic regions of Japan, western Africa, the Caribbean, and South America
- Develops in 2-7% of HTLV-1 infected during 6th-7th decades
- Usually fatal with poor survival with low median survival

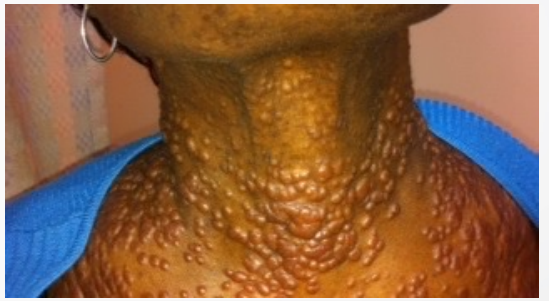


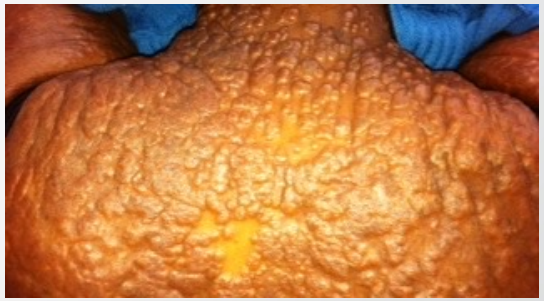


ATLL Sub-classification: Shimoyama Criteria

- **Aggressive subtypes**: frequent hypercalcemia and high LDH
  - Acute type:
    - Leukemia phase
    - Multi-organ involvement







Images: University of Miami

  - Lymphomatous type: <1% leukemic cells

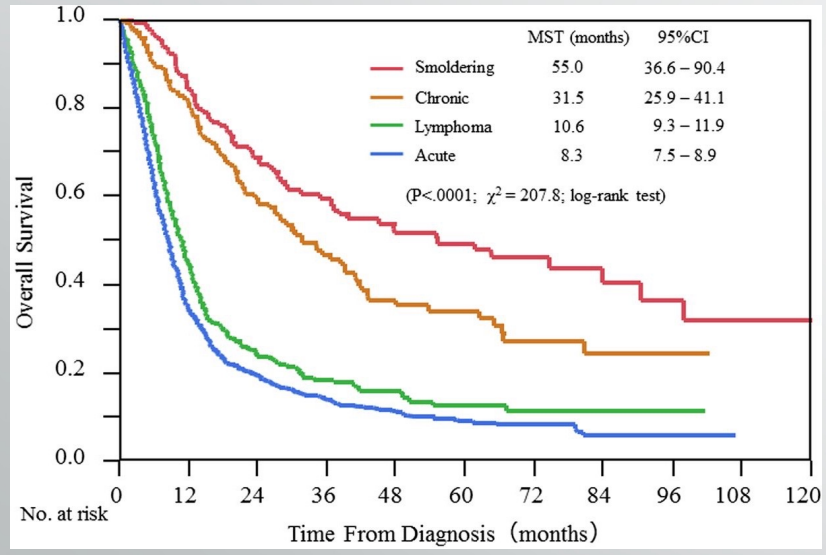
- **"Indolent" subtypes**: least common presentation
  - Smoldering: <5% leukemic cells, LDH < 1.5 x normal, +/- skin and lung involvement
  - Chronic: leukemic phase, normal LDH, +/- lymph nodes, skin, or lung involvement
    - *Unfavorable chronic type variant*: ↑LDH (< 2x normal) behaves more aggressive

ATLL Prognosis: Poor Outcomes Despite Modern Standard Therapies

Japan experience:

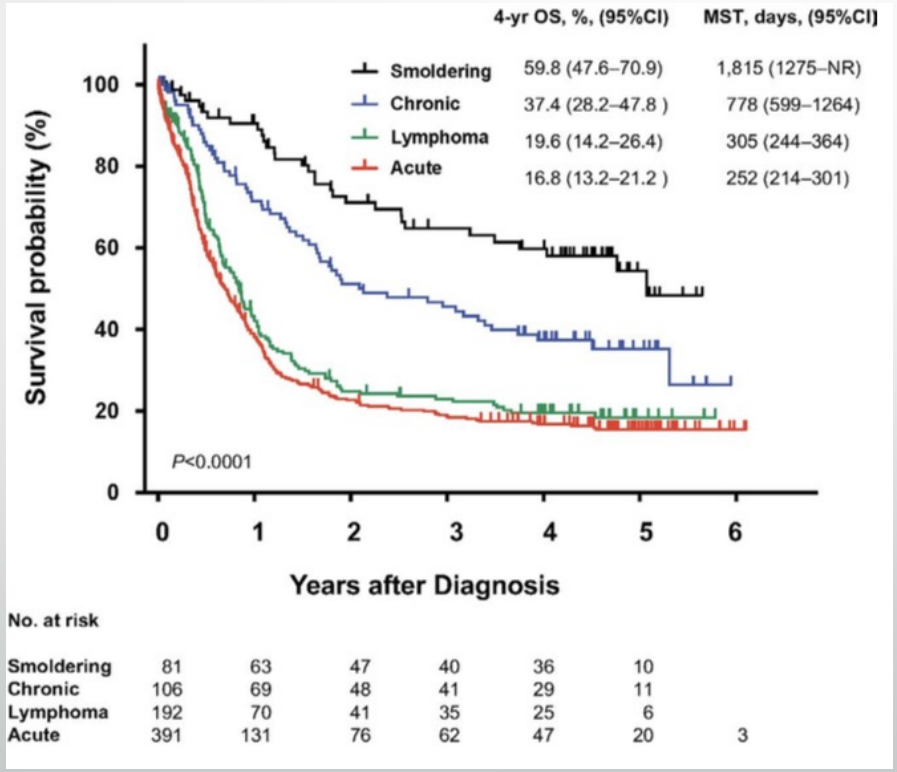
Katsuya et al. *Blood* 2015

N=1594 (Years 2000-2009)



Imaizumi et al. *Cancer Science* 2020

N= 770 (Years 2010-2017)



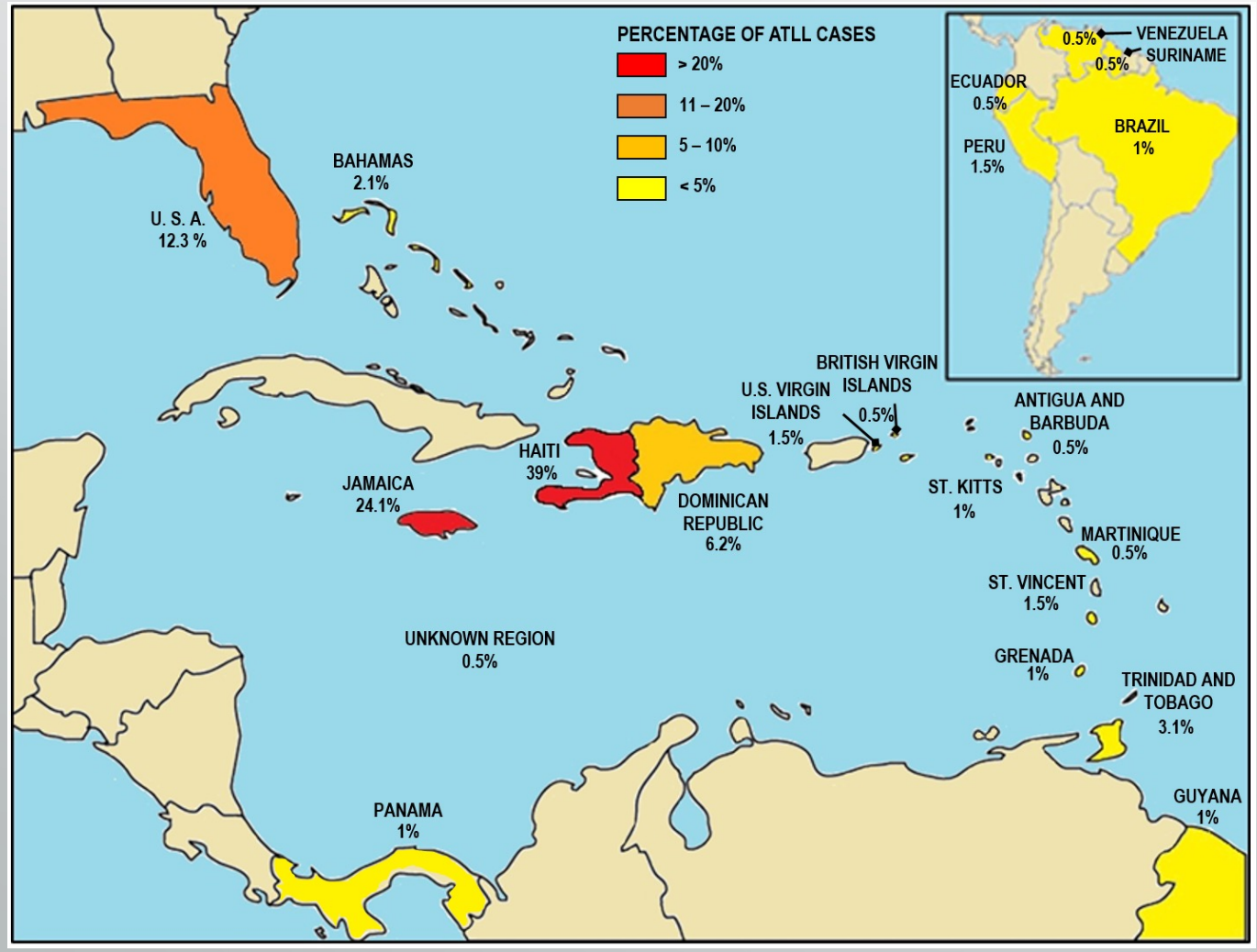
Median Survival:

- Acute type: < 9 months
- Lymphomatous: < 12 months
- Chronic: 26-31 months
- Smoldering: 55-61 months

❖ < 6 months after allogeneic stem cell transplant

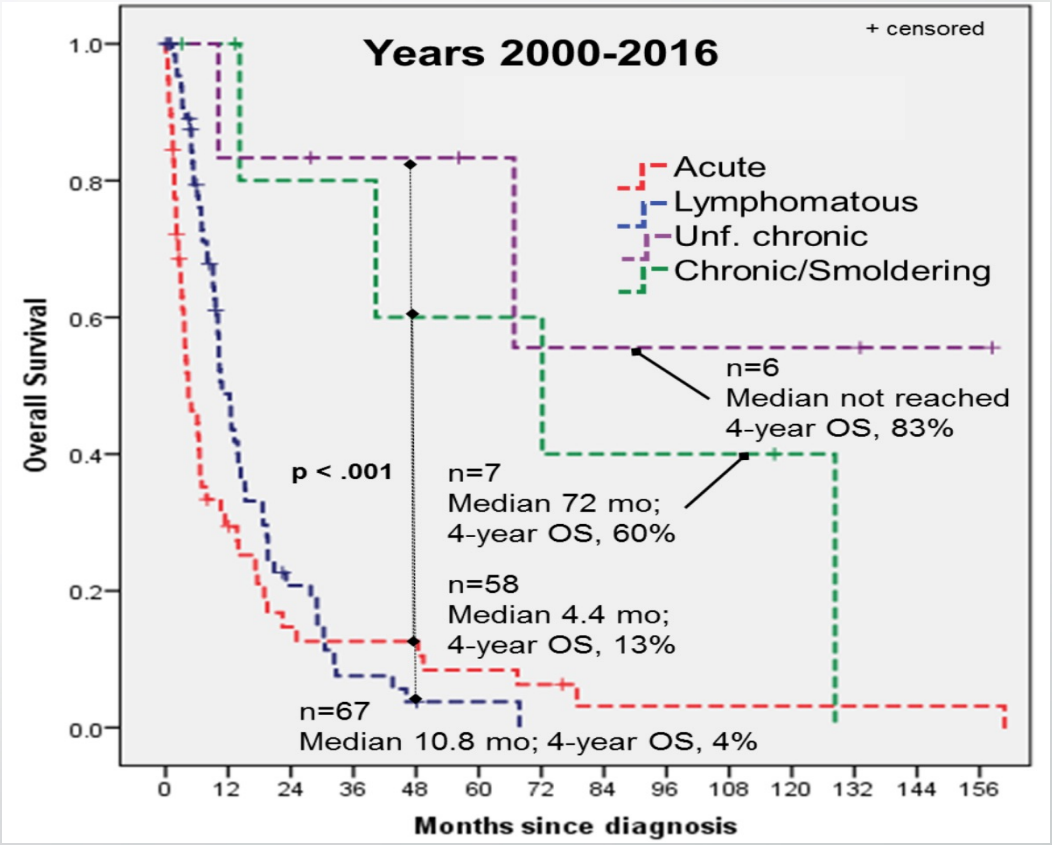
ATLL Experience in Miami

N= 195 patients (Median age 52, HIV co-infection in 9%)



Ramos et al. *Blood Advances* 2018

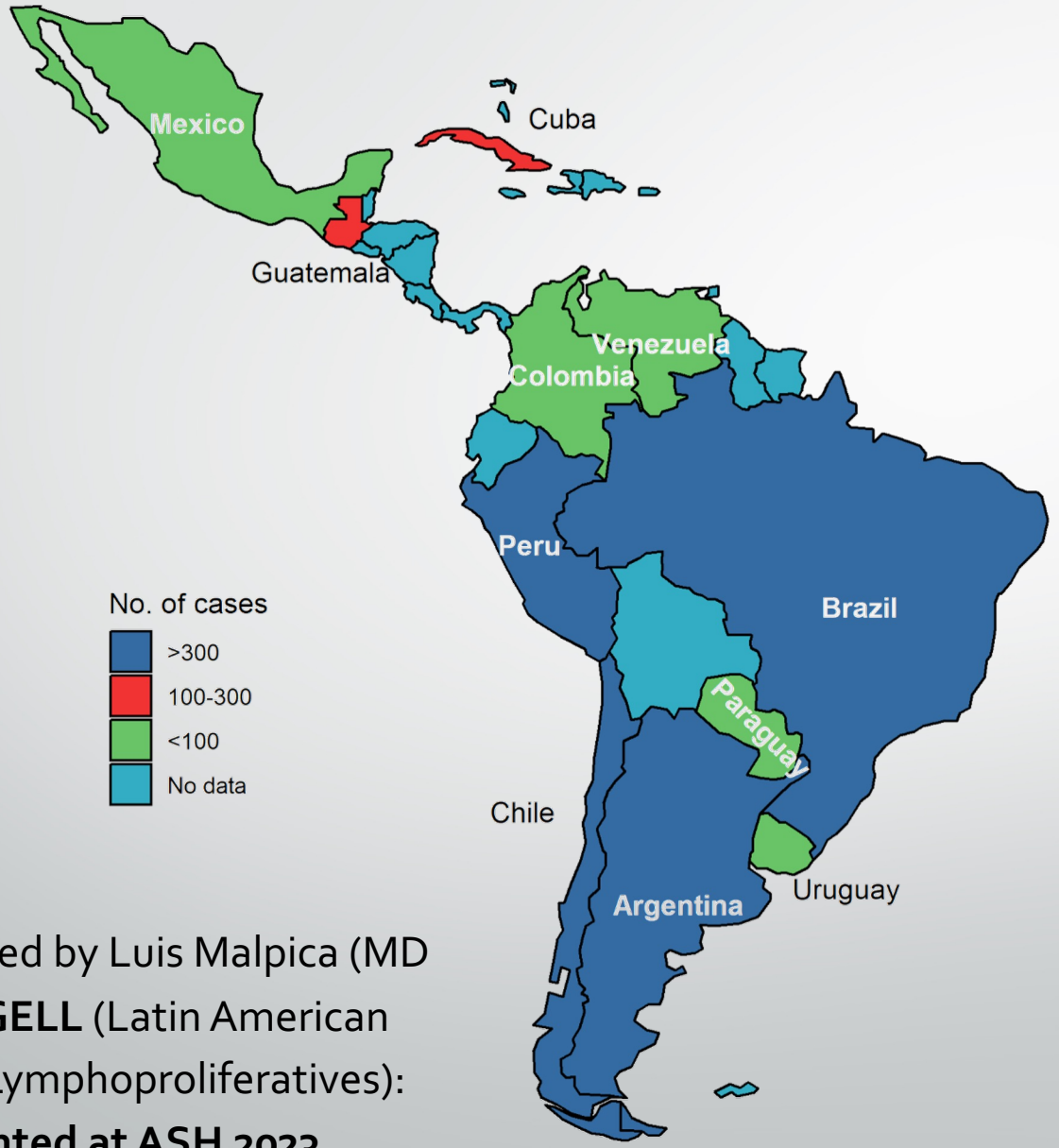
N=138 (Years 2000-2016)

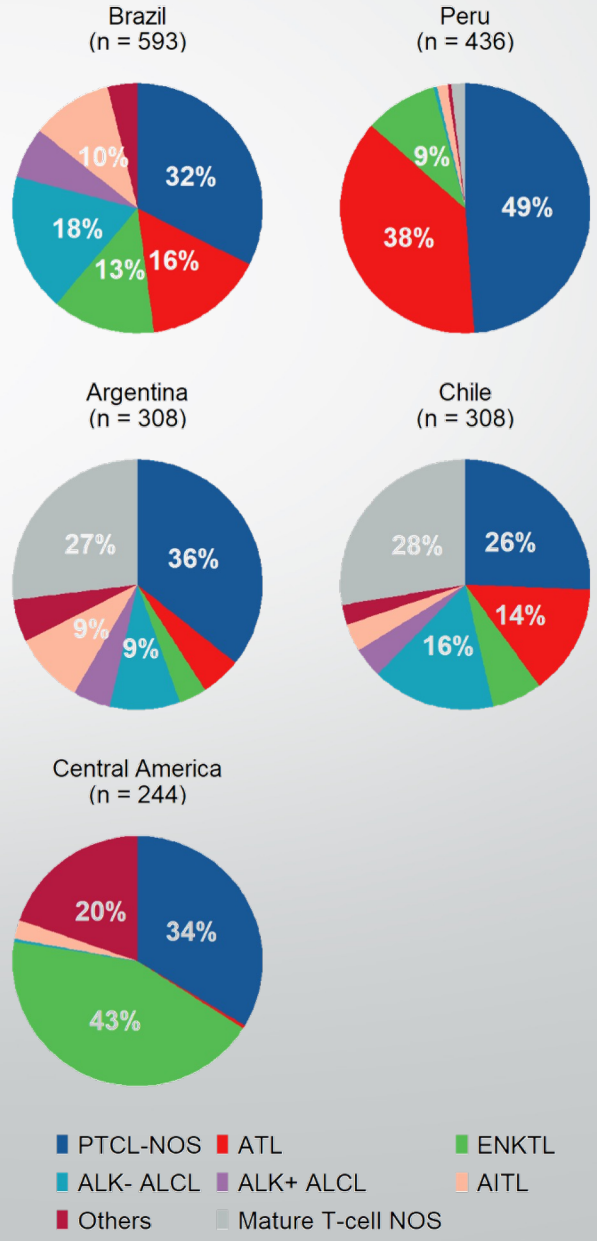


4-yr Overall Survival:

- Acute (n=58): 13%
- Lymphomatous (n=67): 4%
- Chronic/Smoldering (n=7): 60%
- Unfavorable chronic (n=6): not reached

Epidemiology of PTCL in Latin America: Highlights higher incidence of ATLL





Data kindly provided by Luis Malpica (MD Anderson) and **GELL** (Latin American Study Group on Lymphoproliferatives):

To be presented at ASH 2023

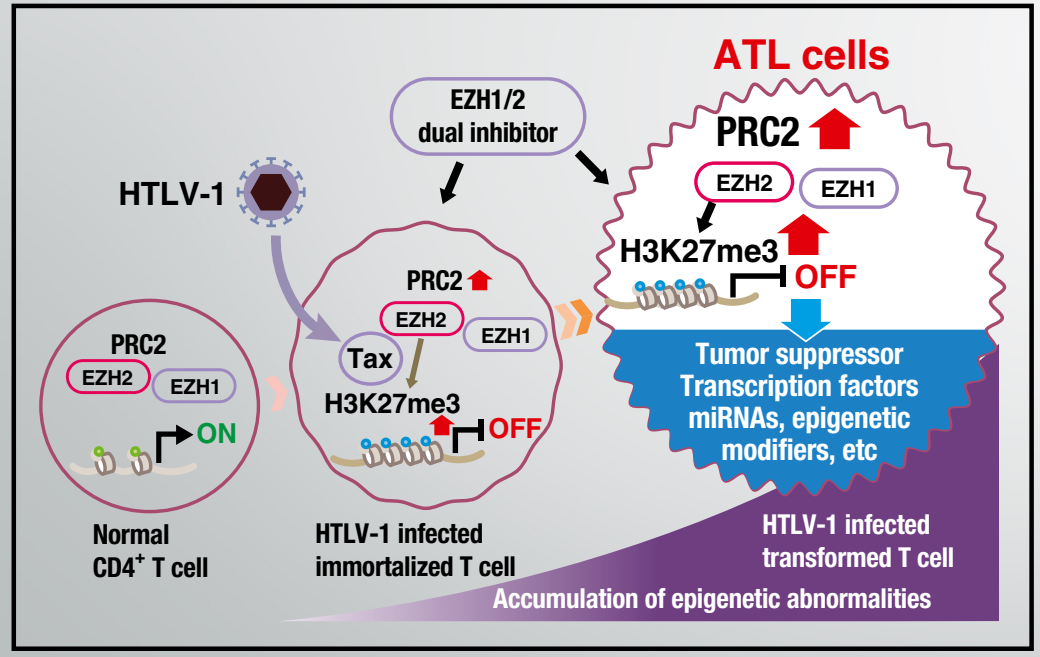
Treatment Options for ATLL

- **First line options:**
  - **Chemotherapy: Followed by allogenic stem cell transplant when feasible!**
  - Standard combination chemotherapy: CHOEP, EPOCH, CHOP-like, hyper cVAD, VCAP-AMP-VECP +/- mogamulizumab (anti-CCR4 antibody, Japan standard, may improve CR rates but without clear survival benefit, and may increase GVHD (morbidity/mortality) in patients who undergo allo-transplant)
  - CHP-brentuximab (anti-CD30 ab-MMAE) (Approved in the U.S. for CD30+ PTCL, benefit of adding BV has has not been clearly established yet for ATLL)
  - Single agents: Oral etoposide (in debilitated patients)
  - **Zidovudine-interferon-α (AZT-IFN): for non-lymphomatous types!**
    - AZT-IFN + $As0_3$: Highly effective in chronic ATLL (Kchour et al. Blood. 2009)
- **Second line options:**
  - **Standard lymphoma regimens:** i.e. ICE, GEMOX, DHA (dexamethasone and cytarabine) + platinum (carboplatin,cisplatin, or oxaliplatin), GDP, GVD
  - **Mogamulizumab:** (Approved in the U.S. for CTCL)
  - **Brentuximab vedotin:** for CD30+ (often used but lack of data in ATLL)
  - **Lenalidomide:** (Approved in Japan, little positive experience in U.S.)
  - **Alemtuzumab:** (anti-CD-52 ab): available as compassionate use in U.S
  - **Single agent chemotherapy:** Oral etoposide, pralatrexate (often used despite lack of efficacy data)
  - **HDAC inhibitors:** i.e. romidepsin, belinostat (these are often used despite lack of efficacy data)

Epigenetic-based Therapies for ATLL

Epigenetic Landscape of ATLL

- Integrative analysis of epigenome (n=3) and transcriptome (n=58)
  - H3K27m3 reprogramed in 54%
  - No EZH2 mutations found

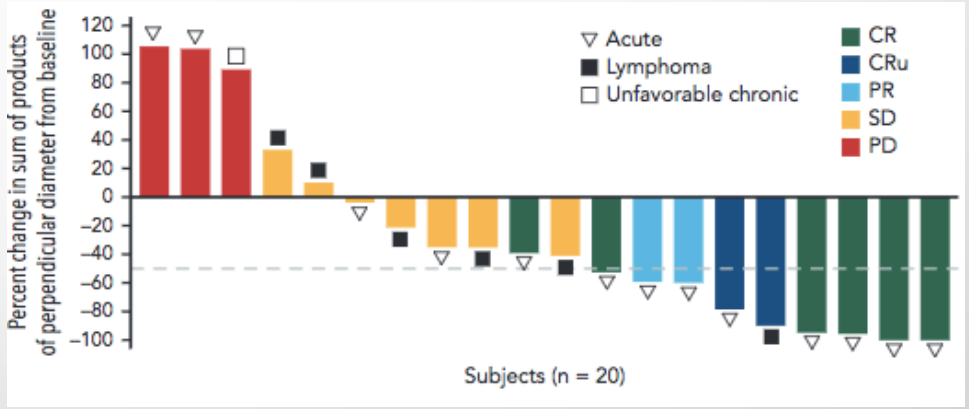


Watanabe [Blood 2017 129(9)]

Epigenetic drug trials for ATLL

- EZH1/2 inhibitor: valemetostat (approved in Japan on Sept. 2022 for R/R ATLL)

  An open-label, single-arm phase 2 trial of valemetostat for R/R refractory ATLL (Izutsu et al. Blood 2023)



  - ORR 46% (CR 20%)
  - Median DOR: not reached
- HDAC inhibitor trials:
  - HBI-8000 (Japan)
  - belinostat+ AZT+ interferon (University of Miami)

Zidovudine (AZT) plus interferon (IFNα)

AZT-FNα can be efficacious in patients with aggressive leukemic ATLL with longer progression-free survival as compared to chemotherapy in patients who achieve a complete response

University of Miami Experience

Complete response (CR) rates

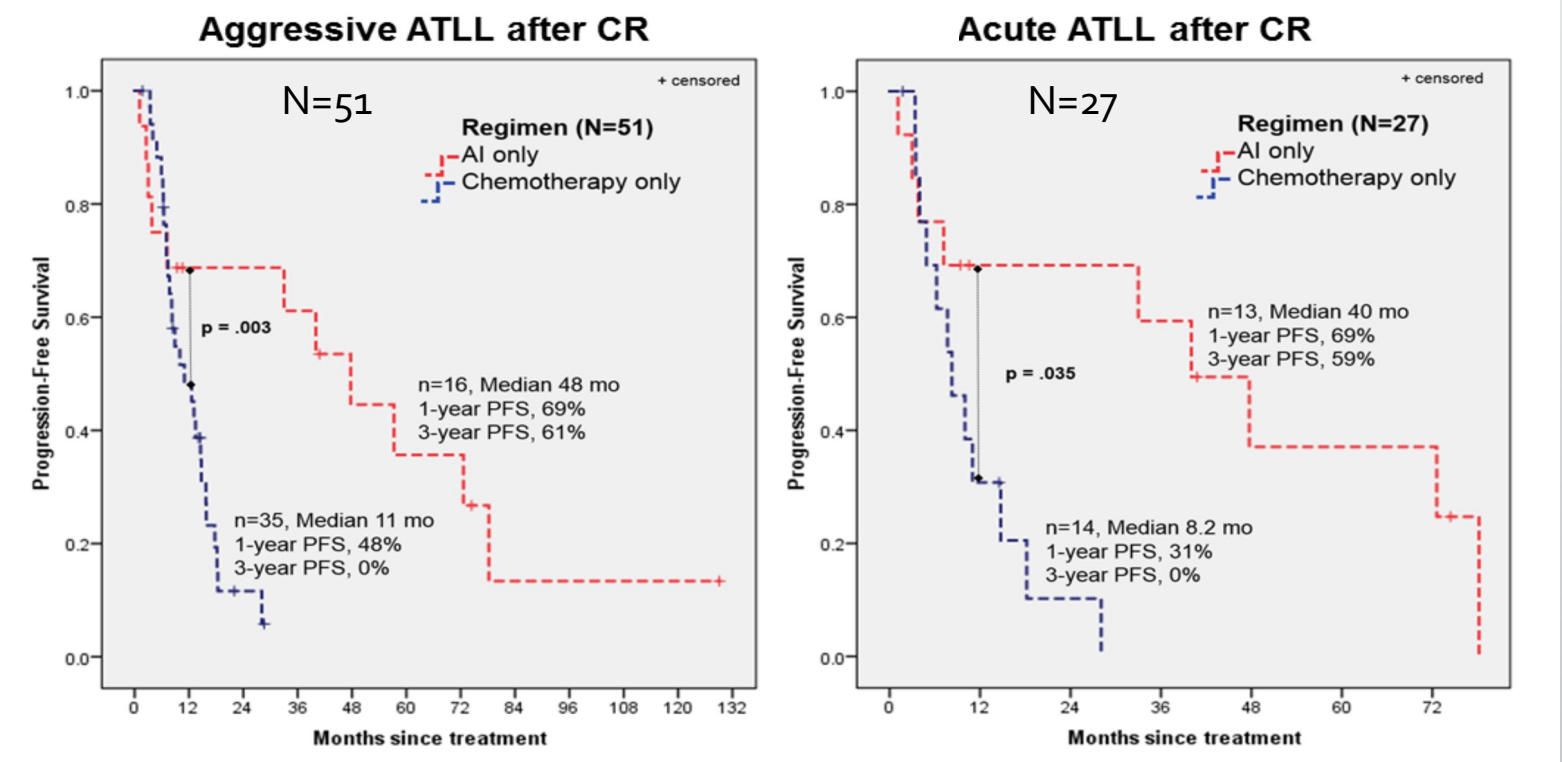
First line chemotherapy:

- Acute: 6/18= 33%
- Lymphomatous: 18/50= 36%

First line AZT-IFN:

- Acute: 10/42= 24%
- Lymphomatous: 1/10= 10%

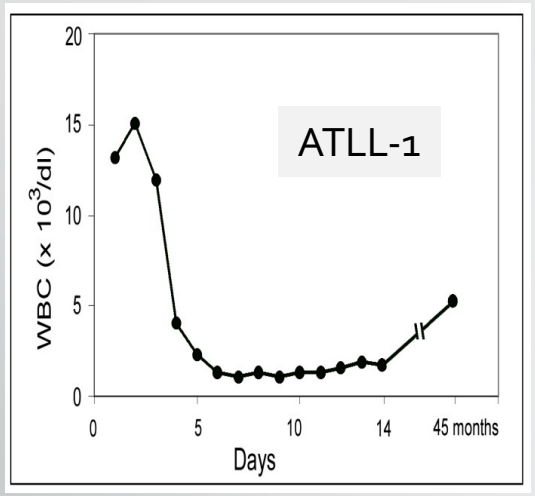
Progression-free survival (PFS) (after first CR)

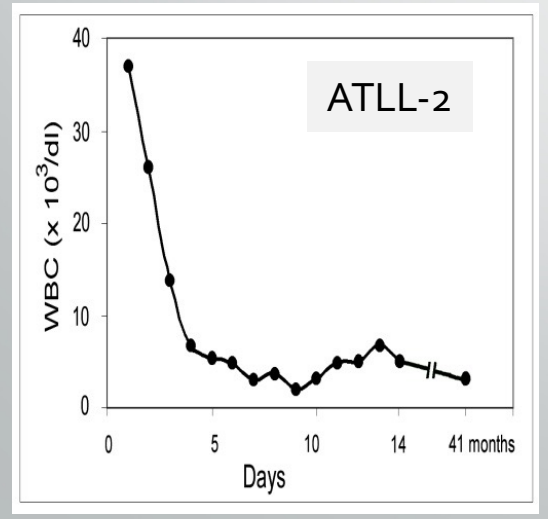


Ramos et al. Blood Adv. 2018 Mar 27;2(6)

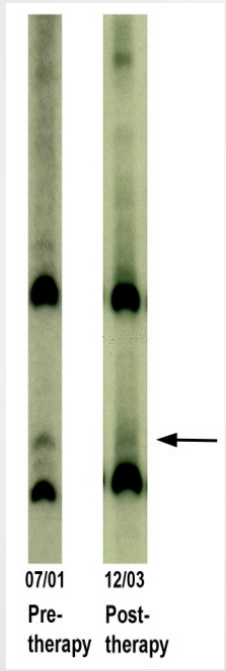
Long-term Responses to AZT/IFN → Persistent molecular disease

Hematologic responses



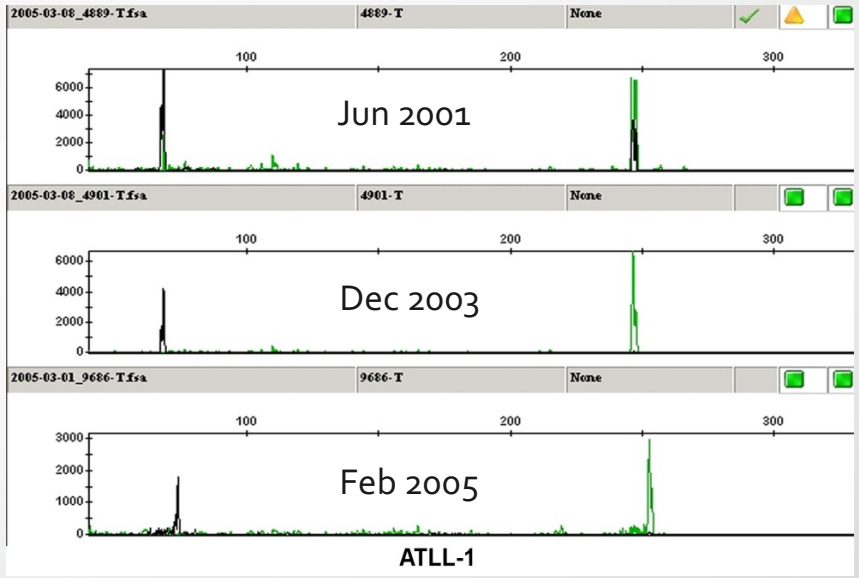


Southern blot

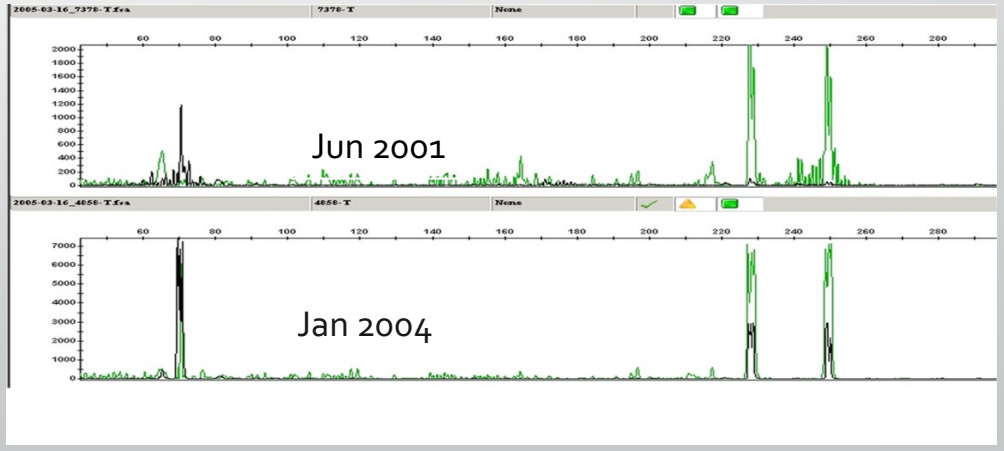


Multiplex PCR for TCR gene rearrangement

ATLL-1



ATLL-2



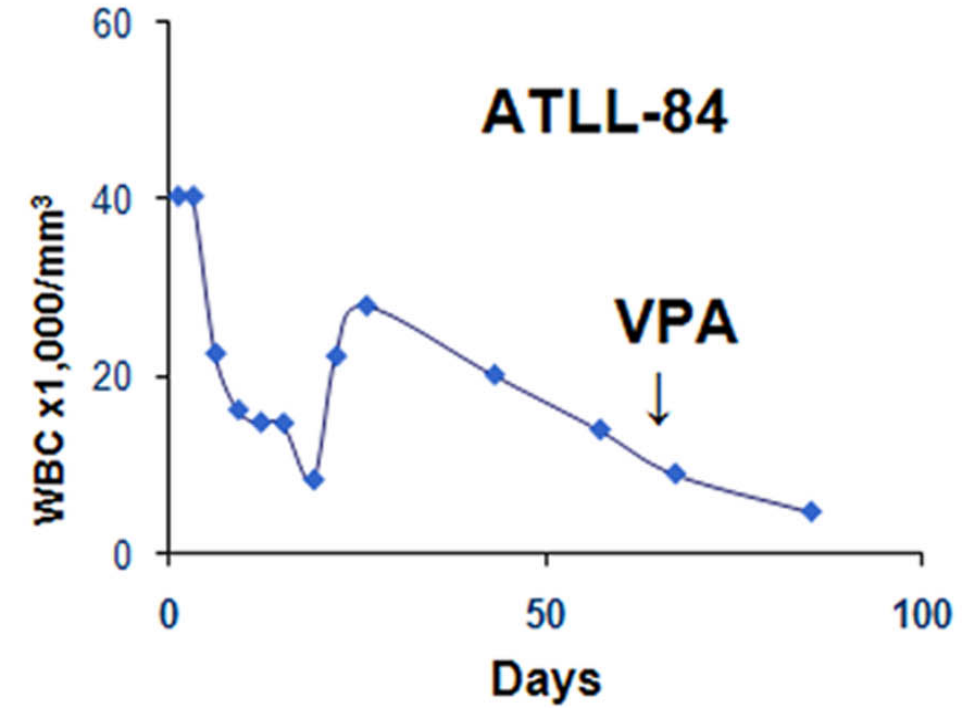
Ramos et al. Blood 2007 Apr 1;109(7)

Molecular Remission in Acute ATLL After Adding Valproic Acid (VPA) to AZT-IFN

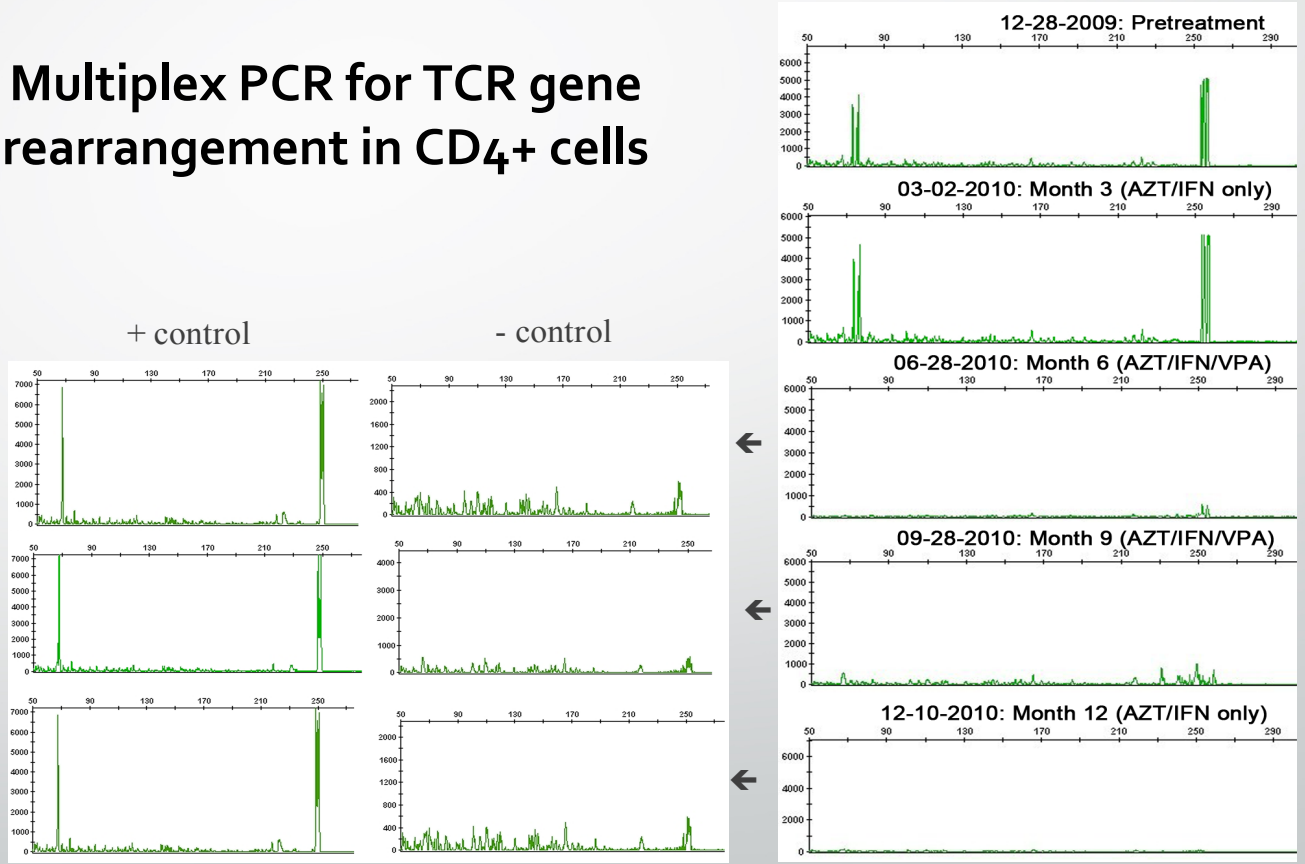
52 y/o Afro-Brazilian presenting with WBC= 240,000, hypercalcemia

Treatment: Leukopheresis → High-dose ZDV/IFN → maintenance ZDV/IFN plus start VPA at day 60

Hematology response



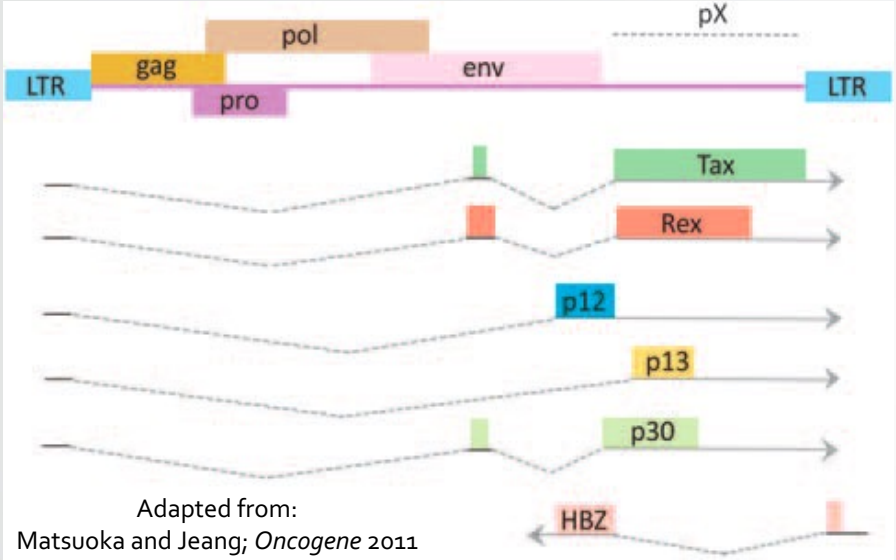
Multiplex PCR for TCR gene rearrangement in CD4+ cells



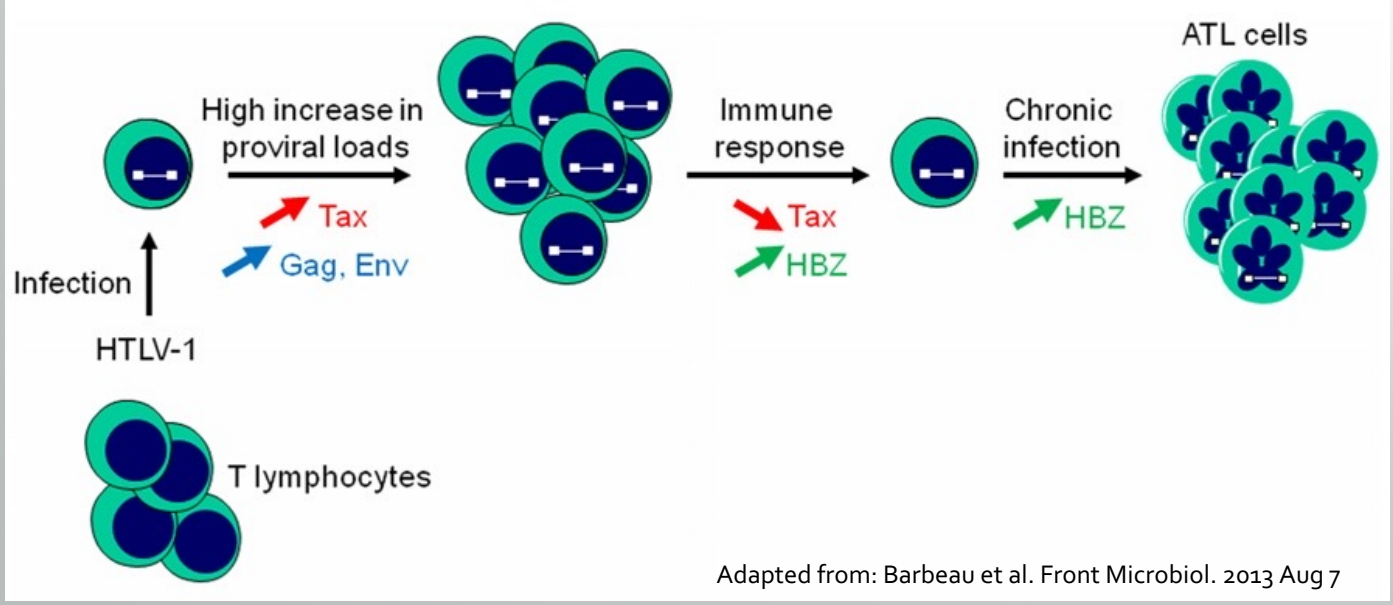
Efficacy data in ClinicalTrials.gov: Identifier NCT00854581

Clonal Evolution of Infected T-cells Leading to ATLL: Loss of Tax but not HBZ

HTLV-1 Provirus



Adapted from:
Matsuoka and Jeang; *Oncogene* 2011



Adapted from: Barbeau et al. Front Microbiol. 2013 Aug 7

Tax:

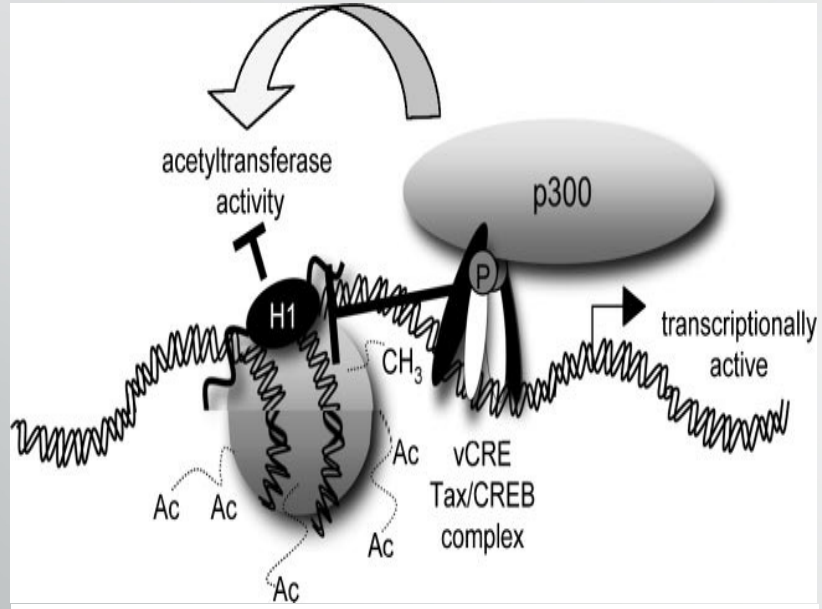
- Has oncogenic activity (e.g . induces NF-κB, blocks P53)
- Highly immunogenic: not expressed in ATLL (Due defective provirus at the 5′ or epigenetic regulation)

HBZ:

- Expressed from negative strand at 3′end
- Expressed in chronically infected T-cells and in ATLL
- Affects a number of signaling pathways and cell proliferation → inhibits senescence (Matsuoka et al., Giam et al)

Targeting HTLV-1/ATLL Using Histone Deacetylase (HDAC) Inhibitors

5′ LTR Regulation by HDACs



Adapted from Konesky et al. JVI 2006

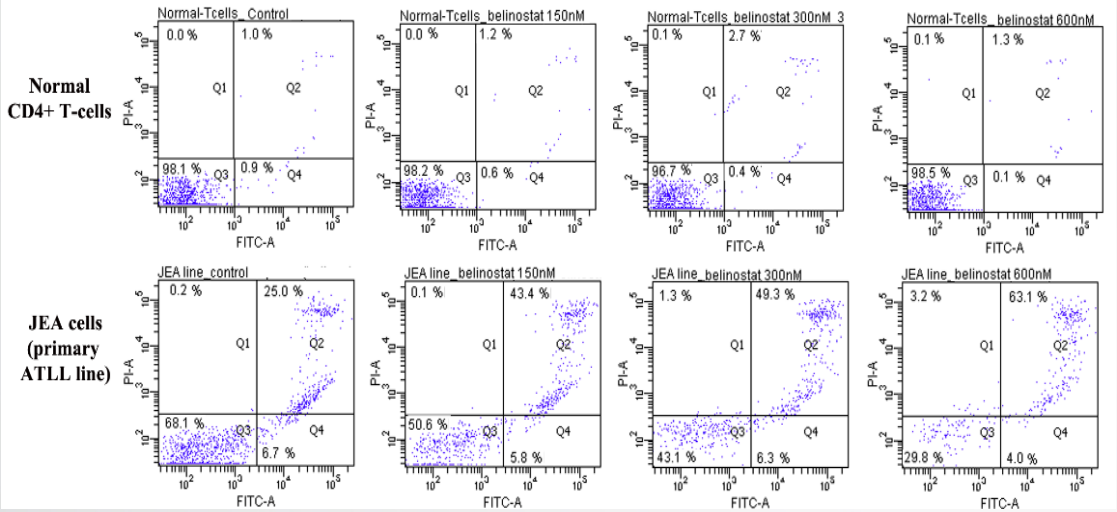
➢ HDAC inhibitors

- Approved second line drugs for T-cell lymphoma
- Reactivate HTLV-1 promoter and Induce Tax expression
- Pre-clinical activity in ATL/HTLV-1 transfected cells and or animal models
  - Desipeptide (Mori et al. 2004, Chen et al. 2009)
  - MS-275, SAHA (vorinostat) (Nishiokita et al. 2008)
  - LBH589 (panabinostat) (Hasegawa et al. 2011)
  - Valproic acid (VPA): **VPA + AZT decreased STLV-1 proviral loads in baboons (Afonso et al. 2010)**

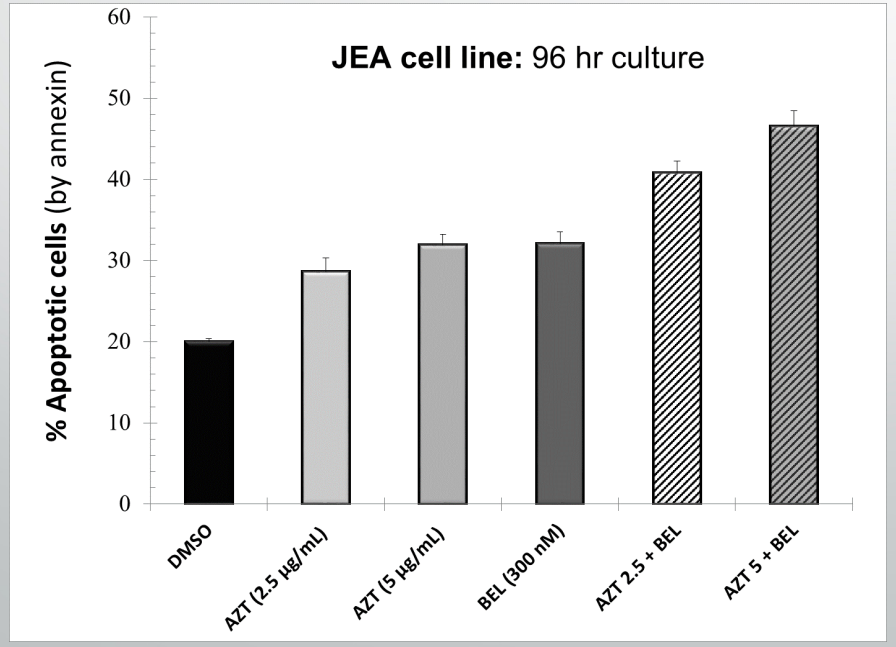
❖ **We hypothesized these drugs could reactivate HTLV-1 in host ATLL cells of subjects treated with AZT-IFN-α thus eliciting anti-HTLV-1/ATL immune responses!**

Belinostat induces dose-dependent apoptosis in ATLL cells (but not normal CD4 T-cells) that is augmented by AZT, blocks HBZ, and induces Tax

Belinostat
150-600 nM

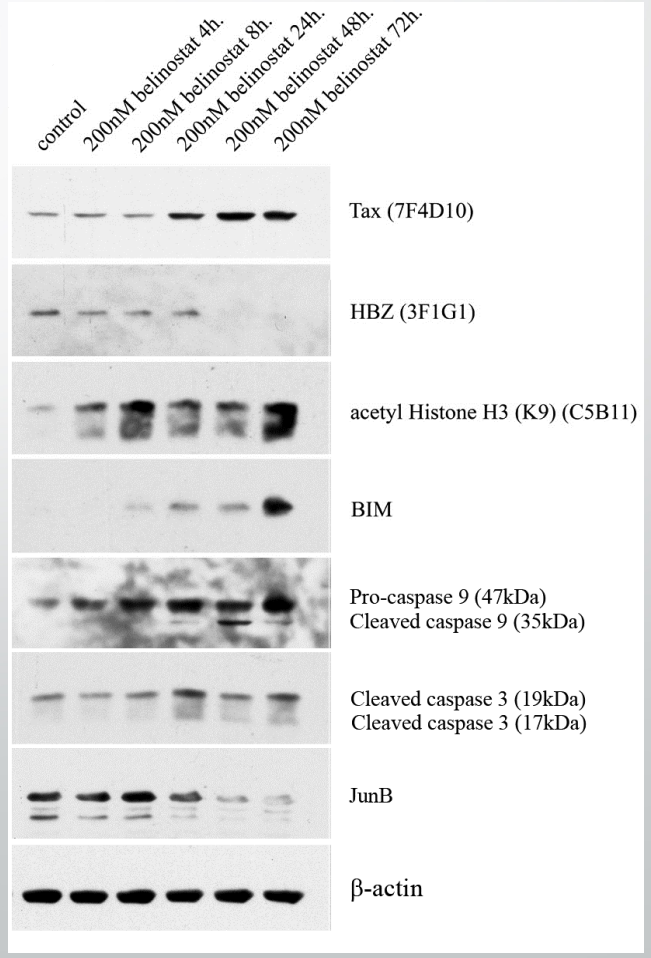


Increasing AZT dose,
constant belinostat



H3 acetylation → ↓ HBZ ↑ Tax
↑ BIM ↓ JunB

ATLL-84c (JEA cell line)



Study Design ClinicalTrials.gov Identifier: NCT02737046

Induction Therapy
AZT-IFN or chemotherapy > 2 weeks

↓

Complete or partial response
(with detectable clonal disease)

↓

Study enrollment

↓

AZT 300 mg orally 3 times daily
Belinostat 1,000 mg/m² on Days 1-5 every 3 weeks x 8 cycles
Optional: Continuation of IFNα

↓

Maintenance Therapy
AZT-IFNα up to the end of Month 12

Inclusion:

- Up to 20 adult participants
- Aggressive ATLL subtypes with persistent histologic, cytologic, or molecular evidence of ATLL in peripheral blood (required prior to enrollment)
- Must have achieved and maintained at least a partial hematologic response to prior AZT/IFNα therapy, chemotherapy, or steroids
- KPS ≥ 50% or ECOG performance status ≤ 3

Primary Objectives:

- **Determine the complete molecular response!**
- Determine the safety

Secondary objectives

- Clinical responses and 1-year survival rates
- Study epigenetic effects
- CTL responses
- Impact on HTLV-1 proviral loads

Interim Results: N=11 acute type ATLL (Presented at 2023 HERN Conference)

PATIENT ID	ATL TYPE	AGE/ SEX	PRIOR THERAPIES	PROTOCOL THERAPY	# CYCLES	BEST RESPONSE	GRADE 3-4 ADVERSE EVENTS	PFS (mo.)	OS (mo.)	STATUS
001	Acute	32 F	AZT-IFNα x 4 mo **Signs of progression after enrollment!**	BEL/ZDV/IFNa2b peg IFNα2b	1	Flare >> Hematologic CR	None	16	37	Dead
002	Acute	67 M	AZT-IFNα x 2wk > ZDV-peg IFNα2b x 6 mo	BEL/ZDV/peg IFNα2b	3	SD (Maintained PR)	Gr 4 neutropenia Gr 3 thrombocytopenia	12	15	Dead
003	Acute	60 M	**Relapsed after** i.v AZT-IFNα x 13 yr, VCAP x 1	BEL/ZDV/IFNα2b	1	PD	None	0.5	8	Dead
004	Acute	45 F	**Relapsed after** i.v. AZT-IFNα x 2 wk, VCAP, ICE, oral etoposide	BEL/ZDV	6	SD Maintained PR	Gr 3 neutropenia Gr 3 thrombocytopenia	5	42	Alive
005	Acute	55 F	AZT-peg IFNα2a x 3 wk	BEL/ZDV/peg IFNa2α	3	CR (molecular)	Gr 4 neutropenia Gr 4 thrombocytopenia	29	29	Alive
006	Acute	71 M	AZT-peg IFNα2a x 3 wk, vincristine x 1	BEL/ZDV/peg IFNa2α	4	PR >> Normal WBC	Gr 4 neutropenia	5	20	Alive
008	Acute	47 M	**Relapsed after** CHOP/CHOEP x 6	BEL/ZDV/peg IFNa2α	2	CR (molecular)	Gr 4 neutropenia Gr 4 thrombocytopenia	9	12	Alive
009	Acute	75 F	**Relapsed after CHOP x 6** ZDV/peg IFNa2α Vincristine/cyclophosphamide x 1 **Signs of progression after enrollment!**	BEL/ZDV/peg IFNa2α	1	PD	Gr 4 neutropenia Gr 4 thrombocytopenia	0.8	`1.3	Dead
010	Acute	36 M	AZT-peg IFNα2a	BEL/ZDV/peg IFNa2α	8	Flare >> PR >>Normal WBC	Gr 4 neutropenia Gr 4 thrombocytopenia	6	6	Alive
011	Acute	41 M	Vincristine/cyclophos/dex AZT-peg IFNα2a **Signs of progression after enrollment!**	BEL/ZDV/peg IFNa2α	3	PR	None	2	2	Alive

Results: Patient 005

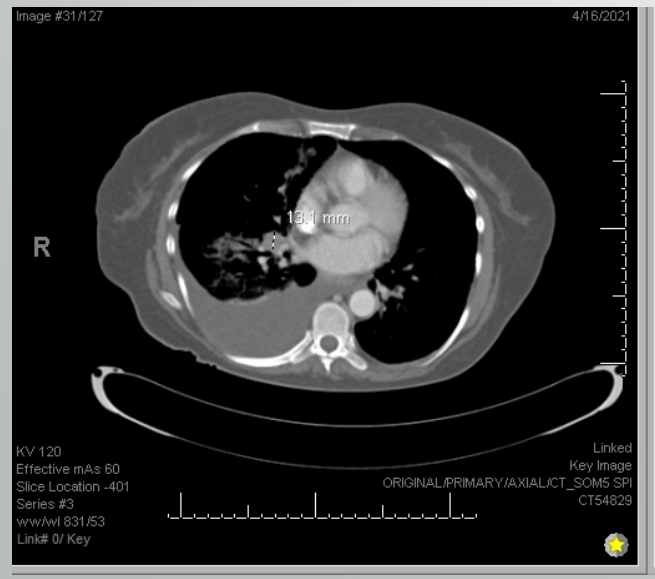
55 y/o Peruvian woman with acute ATLL, WBC=20,000 (86% lymphs), LDH 488 (UNL 214), right hilar mass, malignant right pleural effusion, and ascites. Bone marrow showed 20% involvement by ATL

- Discontinuation of therapy after 3 cycles due to cytopenias
- Persistent bone marrow involvement) (10%) at Month 4

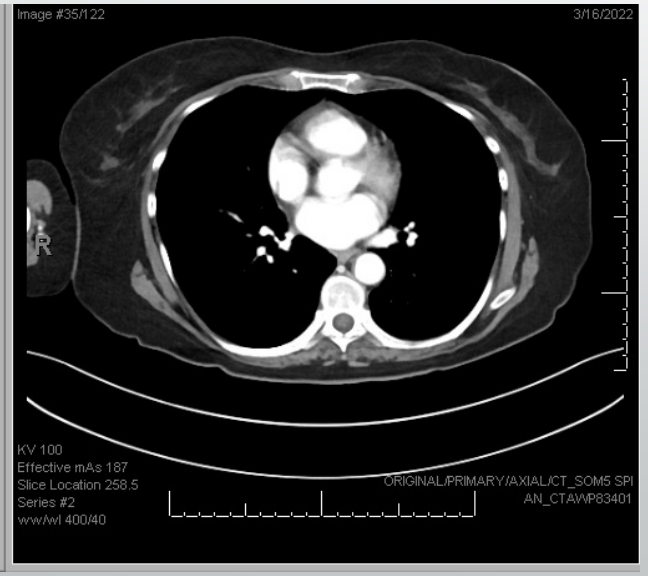
Spontaneous molecular remission!

- Repeat bone marrow biopsy at Month 5 showed no evidence of molecular disease
- Recovery from cytopenias (Month 8: re-started peg-interferon only)
- Continues in remission without clonal evidence of disease after 30 months

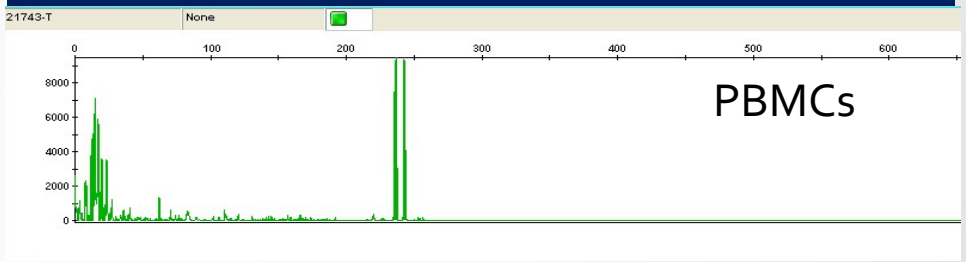
Baseline



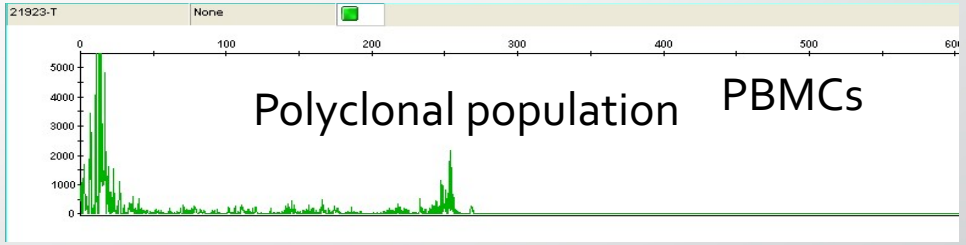
Month 12



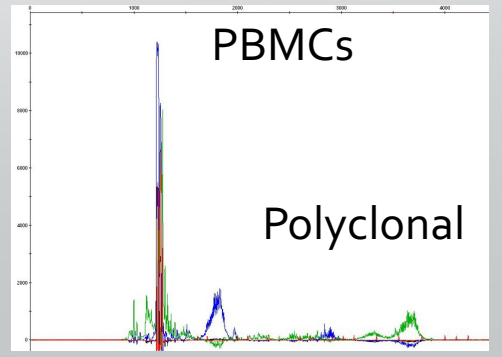
Prior to belinostat

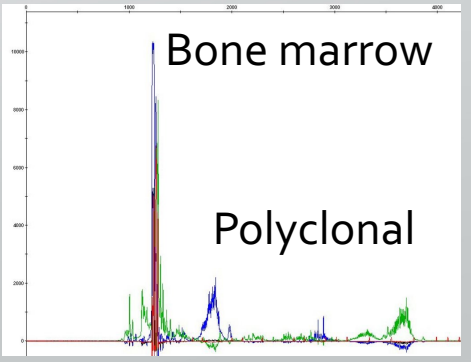


Month 5



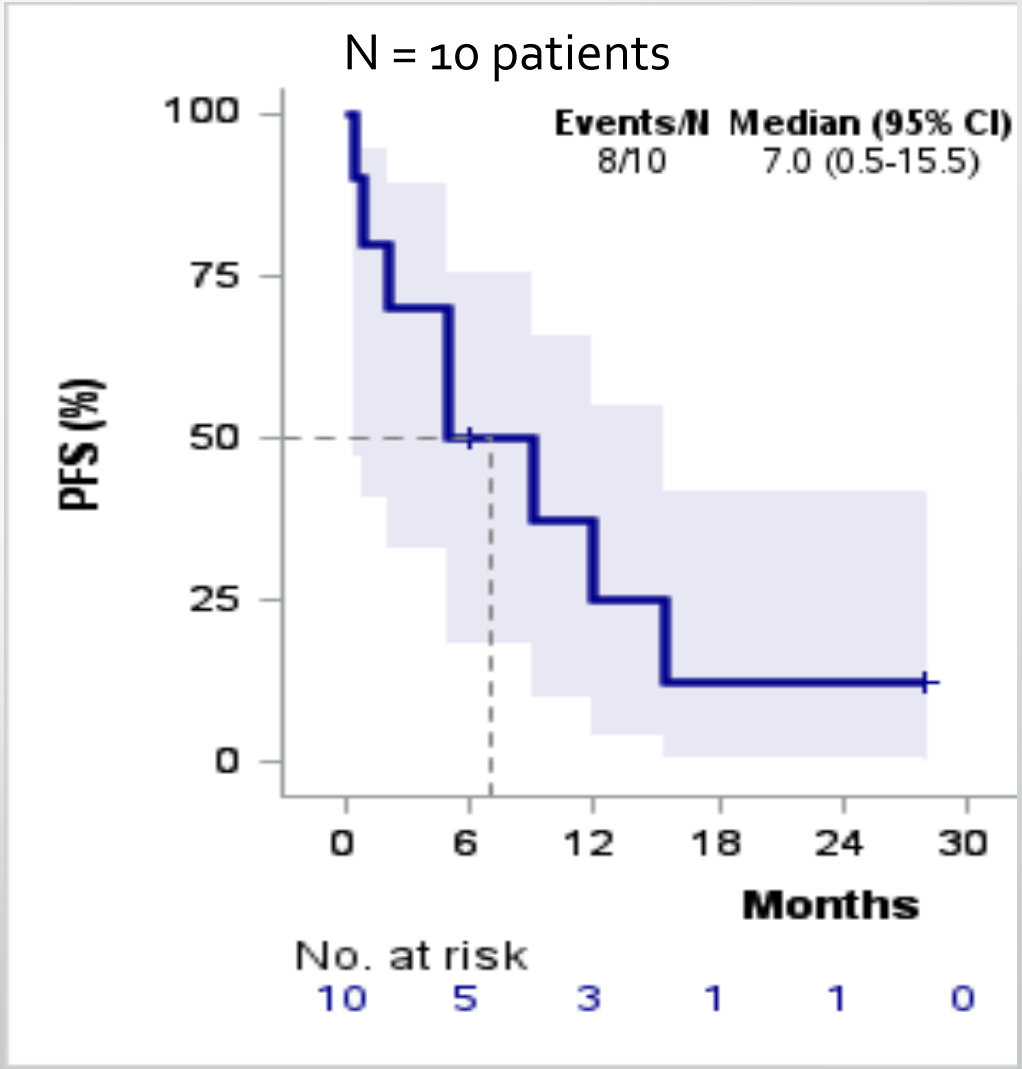
Month 12





Summary on Preliminary Efficacy

- **Response rates:** 2 complete responses (CR) + 3 partial responses (PR) = 50%, 2 stable disease (also included relapsed cases)
  - **Complete hematologic molecular responses in peripheral blood**: 3/10 evaluable patients (30%, including one relapsed case)
    - ❖ Spontaneously seen <u>after</u> treatment discontinuation!
- **Median progression-free survival (PFS):** 7 months (superior to historical ATLL trials)
- **Survival:** 60% of patients (6/10) still alive (range 4-31 months)



Conclusions

- T-cell lymphomas are comprised of heterogenous entities under an already garden-variety cell type category
- Except for ALCL, aggressive T-cell lymphomas carry relatively poor outcomes, thus there is an urgent need to advance treatment
- Tumor specific genetic lesions have been identified though genomic studies that could be exploited therapeutically
- Future clinical trials on aggressive T-cell lymphoma should be hypothesis-driven therapies targeting specific subtypes as suppose to one therapy fitting all
- For ATLL:
  - Poor outcomes continue in the era of modern therapies and emerging treatments
  - AZT-IFN-belinostat demonstrated preliminary efficacy, and that it is relatively safe to administer; expected hematologic adverse events may warrant dose-adjustments
    - Deep molecular responses can be achieved in patients with acute type ATLL
    - Pegylated IFN is clinically active!!!
    - Interim results from phase 2 results warrant testing this regimes as 1st line therapy in the near future