



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

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

Workshop 4

Preclinical models, clinical guidelines, and trials

Moderators: *Luis Malpica & R. Alejandro Sica*



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US National Cancer Research Network (NCCN) guidelines

Steven Horwitz
Memorial Sloan Kettering Cancer Center, USA

NCCN (National Comprehensive Cancer Network) Guidelines For ATLL

Steven M. Horwitz M.D.

Nonna's Garden Chair

Member and Attending Physician

Memorial Sloan Kettering Cancer Center

Professor of Medicine

Weill Cornell Medical College, Cornell University

NCCN Guidelines For ATLL

- NCCN/Committee membership
- Guideline process
- Overview of guidelines

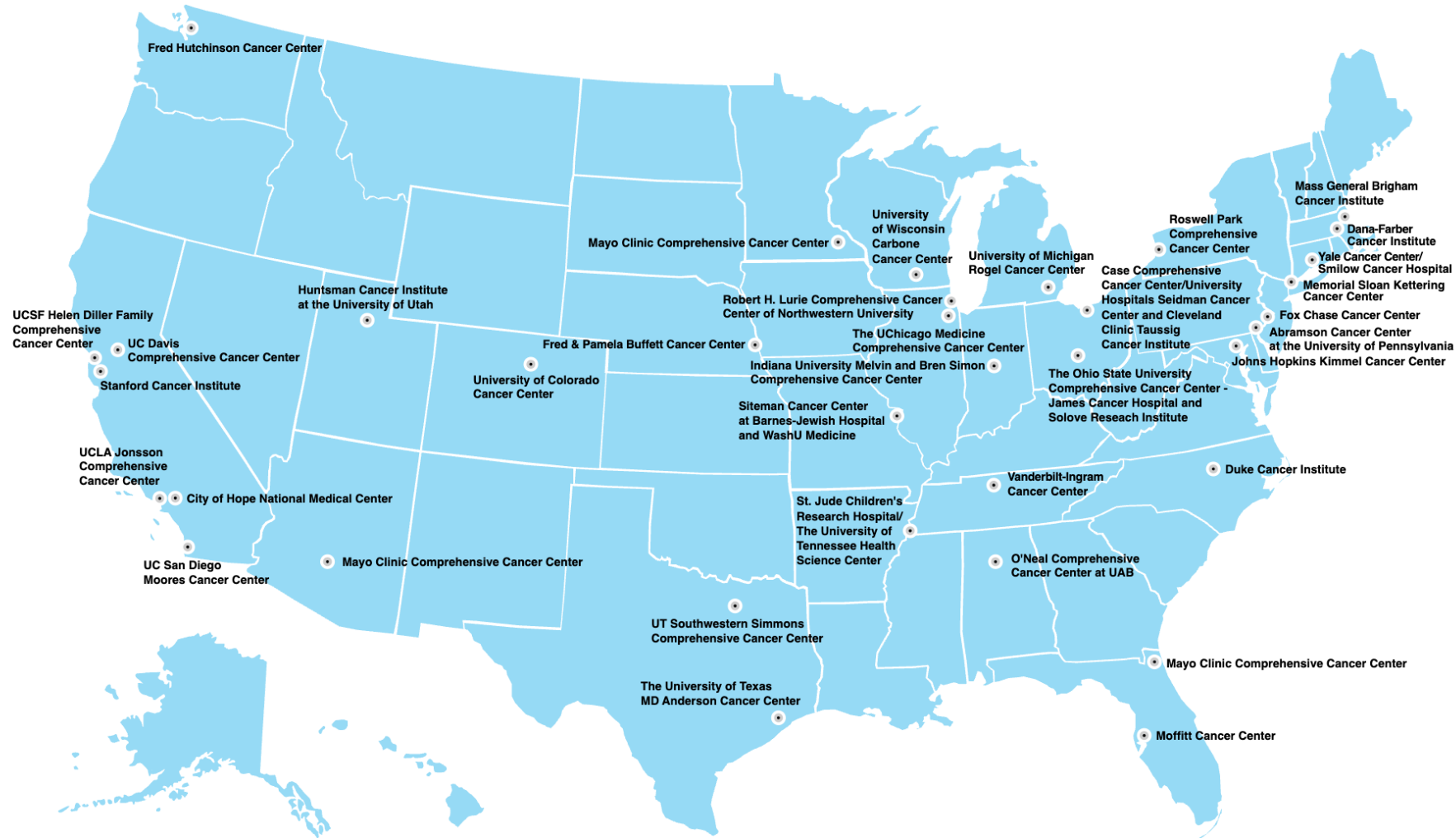
Who Makes Up the NCCN Lymphoma Panel?

- Representatives (N=1) from each member institution
- Multi-disciplinary (T cell and Cutaneous Lymphomas) with representation from:
 - Pathology
 - Radiation oncology
 - Medical oncology/Hematology
 - Dermatology
 - Dermatopathology
 - Bone Marrow Transplant
 - Patient representative
 - Plastic surgery
- Additional members are included if they have specialized expertise in less common forms of lymphoma

Member Institutions



National Comprehensive
Cancer Network®





NCCN Guidelines Version 2.2026

T-Cell Lymphomas

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Susan Thornton ¥
Patient advocate

Carlos Torres-Cabala, MD ≠
The University of Texas
MD Anderson Cancer Center

Ryan Wilcox, MD, PhD † ‡
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Peggy Wu, MD, MPH ☉
UC Davis Comprehensive Cancer Center

Yumeng Zhang, MD ‡
Moffitt Cancer Center

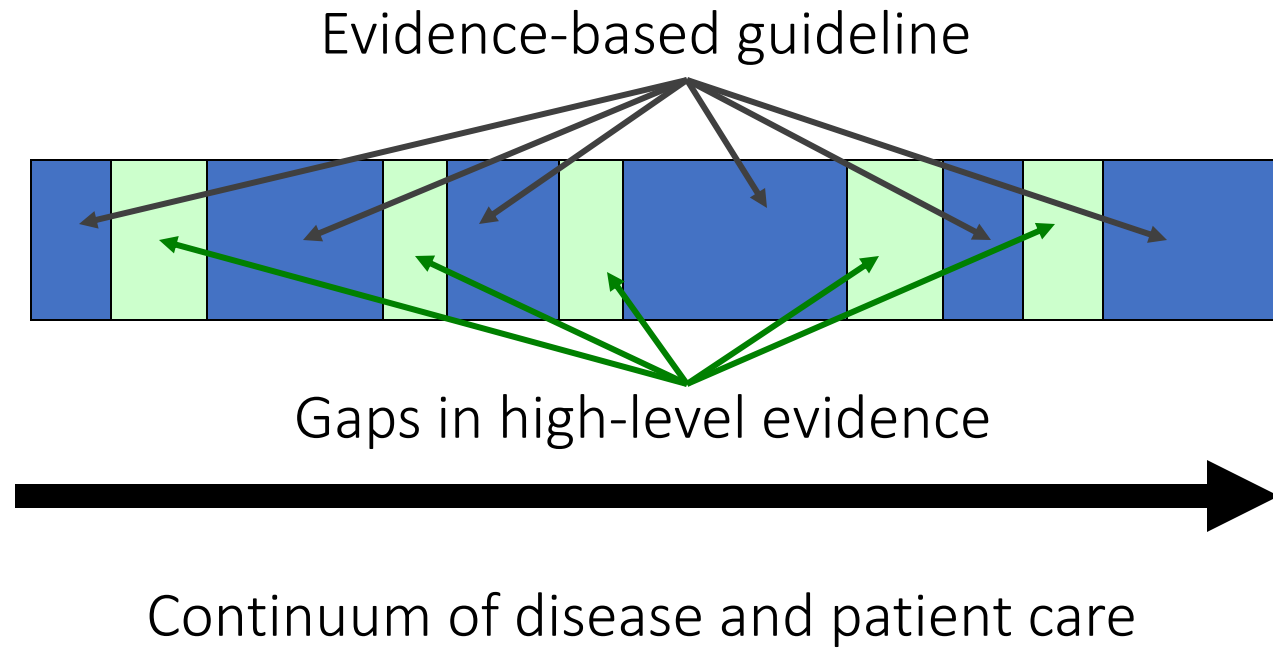
NCCN
Mary Dwyer, MS
Nicholas Sansone, MFA
Hema Sundar, PhD

§ Bone marrow transplantation	≠ Pathology
☉ Dermatology	¥ Patient advocacy
‡ Hematology/Hematology oncology	○ Plastic surgery
♠ Internal medicine	§ Radiotherapy/Radiation oncology
† Medical oncology	* Discussion Section Writing Committee Member

IOM: Guidelines We Can Trust

- Be based on a systematic review of the existing evidence
- Be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups
- Consider important patient subgroups and patient preferences, as appropriate
- Be based on an explicit and transparent process that minimizes distortions, biases, and conflicts of interest
- Provide a clear explanation of the logical relationships between alternative care options and health outcomes, and provide ratings of both the quality of evidence and the strength of recommendations
- Be reconsidered and revised as appropriate when important new evidence warrants modifications of recommendations.

Evidence-based Consensus Allows Comprehensive Guideline



High-level evidence exists



Gaps in evidence filled with expert consensus

NCCN Levels of Evidence

Category 1 The recommendation is based on high level evidence* and there is uniform NCCN consensus ($\geq 85\%$) that the intervention is appropriate.

Category 2A The recommendation is based on lower level evidence** and there is uniform NCCN consensus ($\geq 85\%$) that the intervention is appropriate. (2A is the default category unless otherwise indicated).

Category 2B The recommendation is based on lower level evidence** and there is NCCN consensus (50%-<85%) that the intervention is appropriate.

Category 3: The recommendation is based on any level of evidence; there is major NCCN disagreement that the intervention is appropriate and $\geq 25\%$.

*Randomized controlled trials or meta-analyses

**Smaller randomized clinical trials, well-designed controlled trials without randomization, well-designed cohort studies

The specific definitions of the NCCN Categories of Preference are:

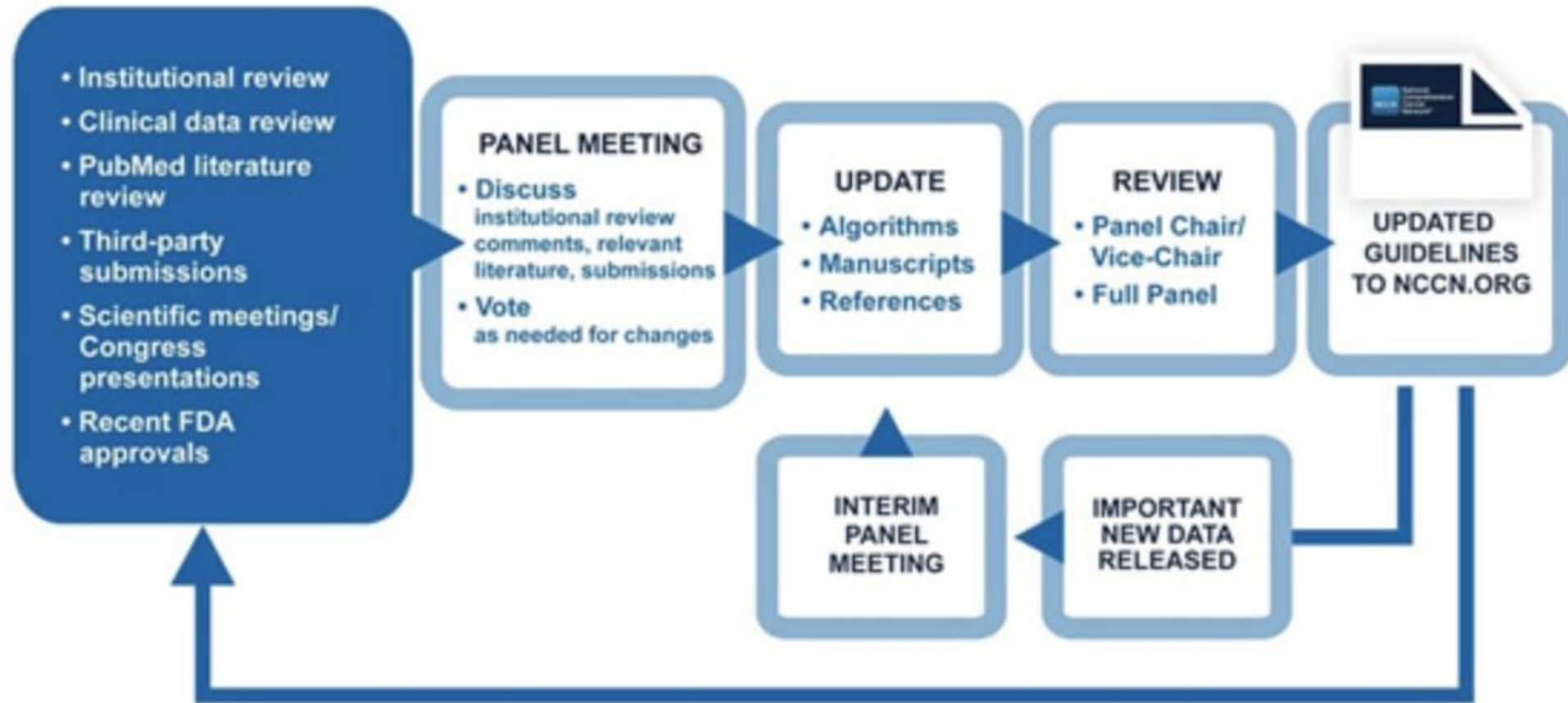
- Preferred intervention: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability
- Other recommended intervention: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes
- Useful in certain circumstances: Other interventions that may be used for select patient populations (defined with recommendation)

All recommendations in the NCCN Guidelines are considered appropriate.

Where does the information come from?

- Randomized controlled trials – definitive and non-definitive
- Meta-analyses
- Non-randomized trials
- Retrospective studies, analyses
- Historical practice patterns
- What *we* do

NCCN Guidelines® Development



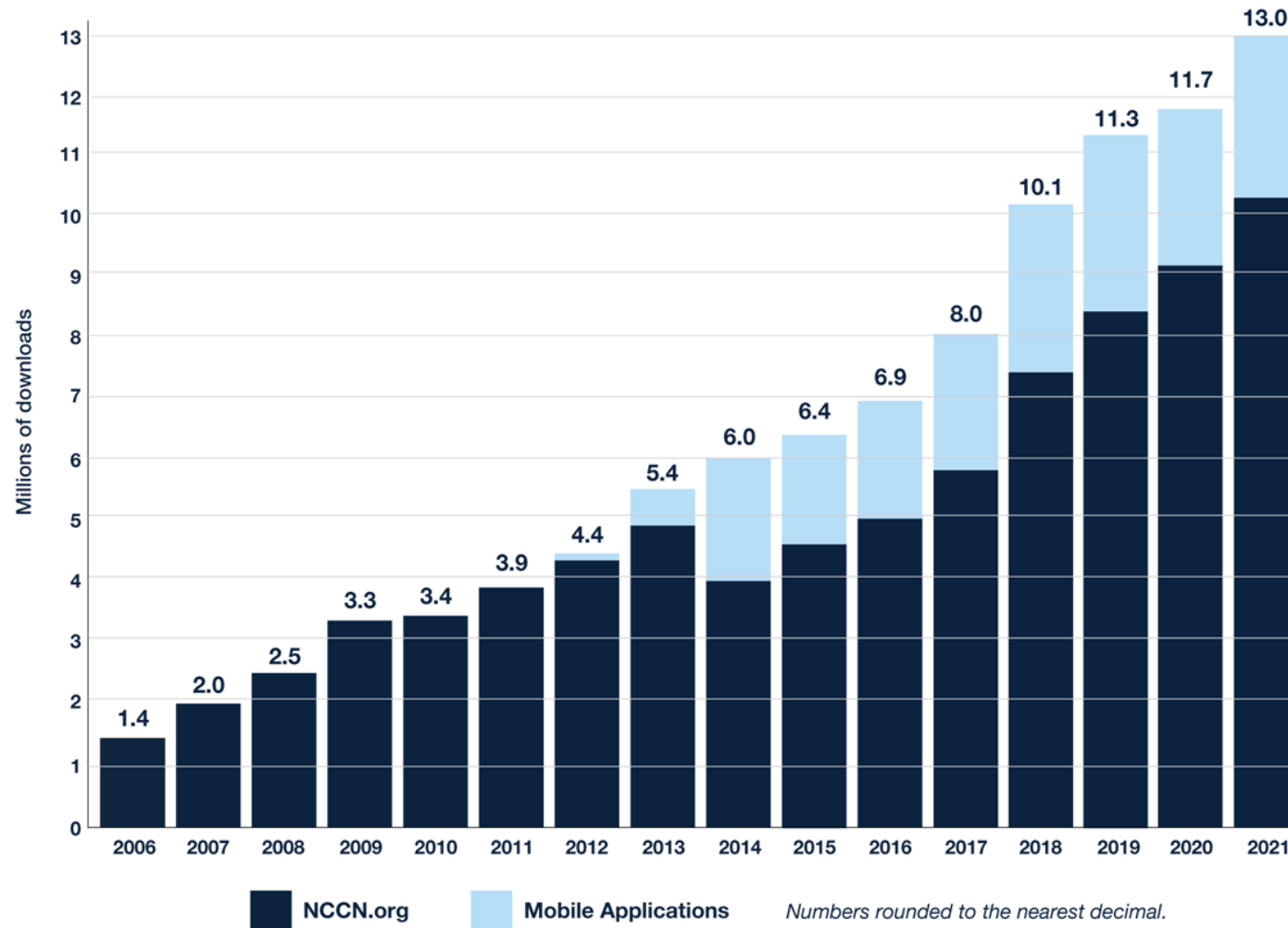
Concurrent development and production of NCCN Guidelines derivative products

Panel votes on all treatment recommendations (and most others) 1 vote /institution

How Do Guidelines Fit into Decisions about Treatment?

- Guidelines are defined for each step in the clinical decision sequence
- One treatment or a range of appropriate treatment options for specific situations may be found in the Guidelines
 - Data may not support a single treatment at a given node
 - Appropriate treatments may be tailored to special populations, e.g. significant co-morbidities which impact on treatment
- The goal is to enhance quality of care by recommending the most appropriate treatment choices
- 100% concordance is usually not appropriate
- Rare diseases = educational component

NCCN Guidelines® Downloads



T-Cell Lymphoma:

2021: 86,914

Primary Cutaneous Lymphomas:

2021: 49,419



DIAGNOSIS^a

ESSENTIAL^b:

- CBC with differential and peripheral blood smear for atypical cells^c: lymphocytosis (ALC >4000/ μ L in adults) in acute and chronic subtypes^d
- Peripheral blood immunophenotyping to establish diagnosis^e
- Flow cytometry panel may include: CD2, CD3, CD4, CD5, CD7, CD8, CD25, CD30, TCR alpha/beta, TRBC1
- Assessment of HTLV-1/2 by serology or other methods^f

USEFUL IN CERTAIN CIRCUMSTANCES:

- Biopsy of lymph nodes (excisional), skin biopsy, GI tract, or bone marrow biopsy^g is required if:
 - Diagnosis is not established on peripheral blood, or
 - Ruling out an underlying infection (eg, tuberculosis, histoplasmosis, toxoplasmosis)
- If biopsy performed, the recommended panel for paraffin section IHC is as follows^{e,h,i}: CD3, CD4, CD5, CD7, CD8, CD25, CD30
- Flow cytometry for CCR4
- Consider MGPT

WORKUP

ESSENTIAL:

- H&P examination, including complete skin examination
- Comprehensive metabolic panel
- LDH
- Serology for strongyloides
- FDG-PET/CT scan^j $\pm$ C/A/P/neck CT with contrast
- Pregnancy testing in those of childbearing potential (if chemotherapy or RT is planned)
- Assess for distress^k

USEFUL IN CERTAIN CIRCUMSTANCES:

- HIV testing
- Hepatitis B and C testing
- CRP, soluble interleukin-2 receptor (sIL-2R), serum albumin, and blood urea nitrogen (BUN)
- Upper GI endoscopy
- Echocardiogram or MUGA scan if anthracycline-based regimen is indicated
- CNS evaluation: Head CT or MRI with contrast and/or lumbar puncture (LP) in all patients with acute or lymphoma subtypes or in patients with neurologic manifestations
- Uric acid
- HLA typing
- Discuss fertility preservation^l

ATLL SUBTYPE^d

Smoldering
subtype ([ATLL-2](#))

Chronic subtype
([ATLL-3](#))

Acute subtype
([ATLL-4](#))

Lymphoma subtype
([ATLL-4](#))

Educational/Reference Material

DIAGNOSTIC CRITERIA FOR ATLL¹

	Smoldering	Chronic	Lymphoma	Acute
Anti-HTLV-1 antibody	+	+	+	+
Lymphocyte (x 10 ⁹ /1/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/1/L)	<2.74	<2.74	*	*
Histology-proven lymphadenopathy	No	*	+	*
Tumor 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	*	*

RESPONSE CRITERIA FOR ATLL¹

Response	Definition	Lymph Nodes	Extranodal Masses	Spleen, Liver	Skin	Peripheral Blood	Bone Marrow
Complete remission*	Disappearance of all disease	Normal	Normal	Normal	Normal	Normal [†]	Normal
Uncertified complete remission*	Stable residual mass in bulky lesion	≥75% decrease [‡]	≥75% decrease [‡]	Normal	Normal	Normal [†]	Normal
Partial remission*	Regression of disease	≥50% decrease [‡]	≥50% decrease [‡]	No increase	≥50% decrease	≥50% decrease	Irrelevant
Stable disease*	Failure to attain complete/partial remission and no progressive disease	No change in size	No change in size	No change in size	No change in size	No change	No change
Relapsed disease or progressive disease	New or increased lesions	New or ≥50% increase [§]	New or ≥50% increase [§]	New or ≥50% increase	≥50% increase	New or ≥50% increase [#]	Reappearance

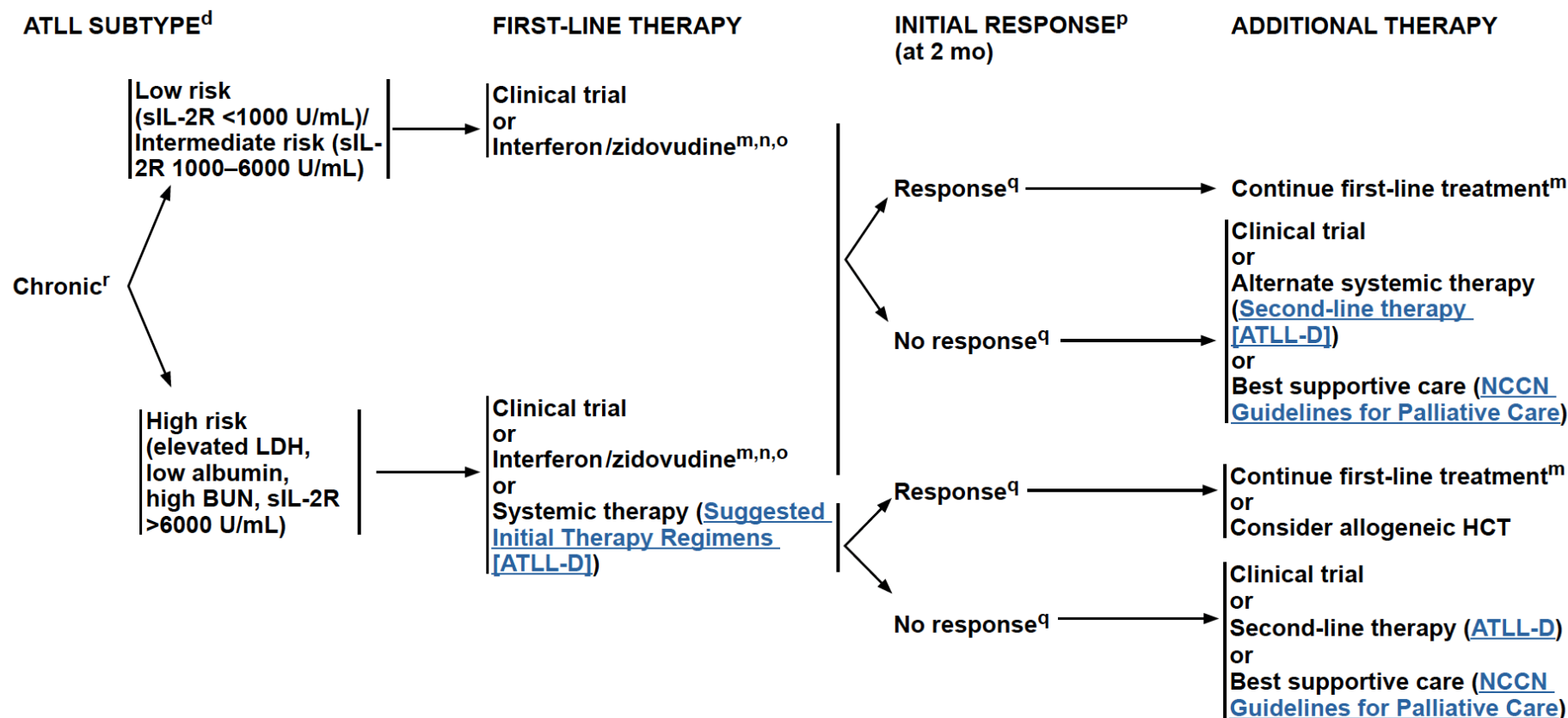
PROGNOSTIC INDEX FOR ACUTE AND LYMPHOMA SUBTYPES

PROGNOSTIC INDEX FOR ACUTE- AND LYMPHOMA-TYPE ATLL (ATL-PI)^a

RISK FACTORS	RISK GROUPS
• Stage III/IV • ECOG PS >1 • Age >70 y • Albumin <3.5 g/dL • sIL-2R >20,000 U/mL	Low 1–2 Intermediate 3–4 High 5–6

MODIFIED PROGNOSTIC INDEX FOR AGGRESSIVE ATLL (AGE <70 Y)^b

RISK FACTORS	RISK GROUPS
• Clinical subtype of acute ATLL • CRP level ≥2.5 mg/dL • ECOG PS 2–4 • sIL-2R >5,000 U/mL • Adjusted Ca level ≥12 mg/dL	Low 0–1 Intermediate 2–3 High 4–5



^d [Diagnostic Criteria for ATLL \(ATLL-A\)](#).

^m Outside of a clinical trial, if the disease is not responding or is progressing within a 2-month period, treatment with zidovudine and interferon should be stopped. If there is evidence of clinical benefit, treatment should continue until best response is achieved. If life-threatening manifestations, treatment can be discontinued before the 2-month period.

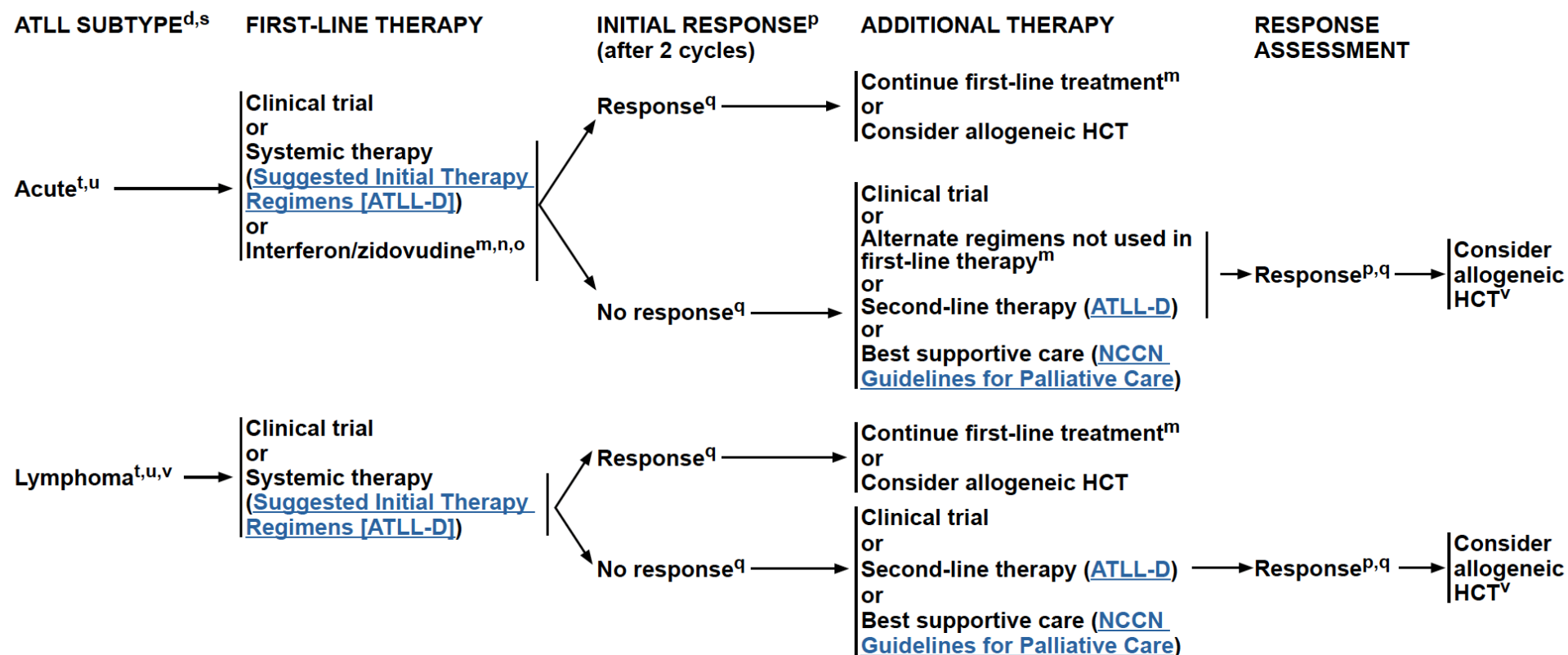
ⁿ See references for zidovudine and interferon ([ATLL-D 2 of 2](#)).

^o Peginterferon alfa-2a or ropeginterferon alfa-2b-njft (if peginterferon alfa-2a is unavailable) may be substituted for other interferon preparations (Schiller M, et al. J Eur Acad Dermatol Venerol 2017;31:1841-1847; Patsatsi A, et al. J Eur Acad Dermatol Venereol 2022;36:e291-e293; Osman S, et al. Dermatol Ther 2023;2023:7171937; Mesa R et al. Ann Hematol 2025;104:2571-2573).

^p If nodal disease is present, repeat C/A/P/neck CT with contrast or FDG-PET/CT. Other baseline imaging studies relevant for response assessment should be repeated as well.

^q See [Response Criteria for ATLL \(ATLL-B\)](#). Responses include CR, uncensored CR, and PR.

^r Prognostic Index for chronic and smoldering ATLL: Katsuya H, et al. Blood 2017;130:39-47.



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^s [Prognostic Index for Acute and Lymphoma Subtypes \(ATLL-C\)](#).

^t CNS disease is common and prophylaxis is recommended.

^u Antiviral therapy alone is not effective.

^v The long-term efficacy of initial therapy regimens is limited. Allogeneic HCT may be a curative option for some patients.



SUGGESTED TREATMENT REGIMENS^{a,b,c}

INITIAL THERAPY

Preferred (alphabetical order)

- Clinical trial
- CHP (Cyclophosphamide/Doxorubicin/Prednisone) + Brentuximab vedotin for CD30+ cases
- CHOP (Cyclophosphamide/Doxorubicin/Vincristine/Prednisone) + Mogamulizumab-kpkc^{d,e} (no intention to proceed to transplant)
- Dose-adjusted EPOCH (Etoposide/Prednisone/Vincristine/Cyclophosphamide/Doxorubicin)
- Interferon/Zidovudine^f (acute, chronic, and symptomatic smoldering subtypes)

Other Recommended (alphabetical order)

- CHOEP (Cyclophosphamide/Doxorubicin/Vincristine/Etoposide/Prednisone)
- HyperCVAD (Cyclophosphamide/Vincristine/Doxorubicin/Dexamethasone) alternating with High-Dose Methotrexate/Cytarabine

Useful in Certain Circumstances

- CHOP (Cyclophosphamide/Doxorubicin/Vincristine/Prednisone) (unable to tolerate intensive regimen or non-CD30 expressing ATLL)

SECOND-LINE THERAPY OR SUBSEQUENT THERAPY

Preferred (alphabetical order)

- Clinical trial
- Single agents
 - Brentuximab vedotin for CD30+ cases
 - Lenalidomide^g
 - Mogamulizumab-kpkc^{d,e,g}
- Combination regimens
 - DHA (Dexamethasone/Cytarabine) + platinum (Carboplatin, Cisplatin, or Oxaliplatin)
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 - GDP (Gemcitabine/Dexamethasone/Cisplatin)
 - GemOx (Gemcitabine/Oxaliplatin)
 - GVD (Gemcitabine/Vinorelbine/Liposomal Doxorubicin)
 - ICE (Ifosfamide/Carboplatin/Etoposide)
 - Interferon/Zidovudine^f (acute, chronic, and symptomatic smoldering subtypes)

Alternative (alphabetical order)

- Single agents
 - Alemtuzumab^h
 - Arsenic trioxide
 - Belinostat
 - Bendamustine
 - Gemcitabine
 - Pralatrexate
 - RT in selected cases with localized, symptomatic diseaseⁱ



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- Discussion section



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Targeting Epigenetic and Other Pathways in ATLL

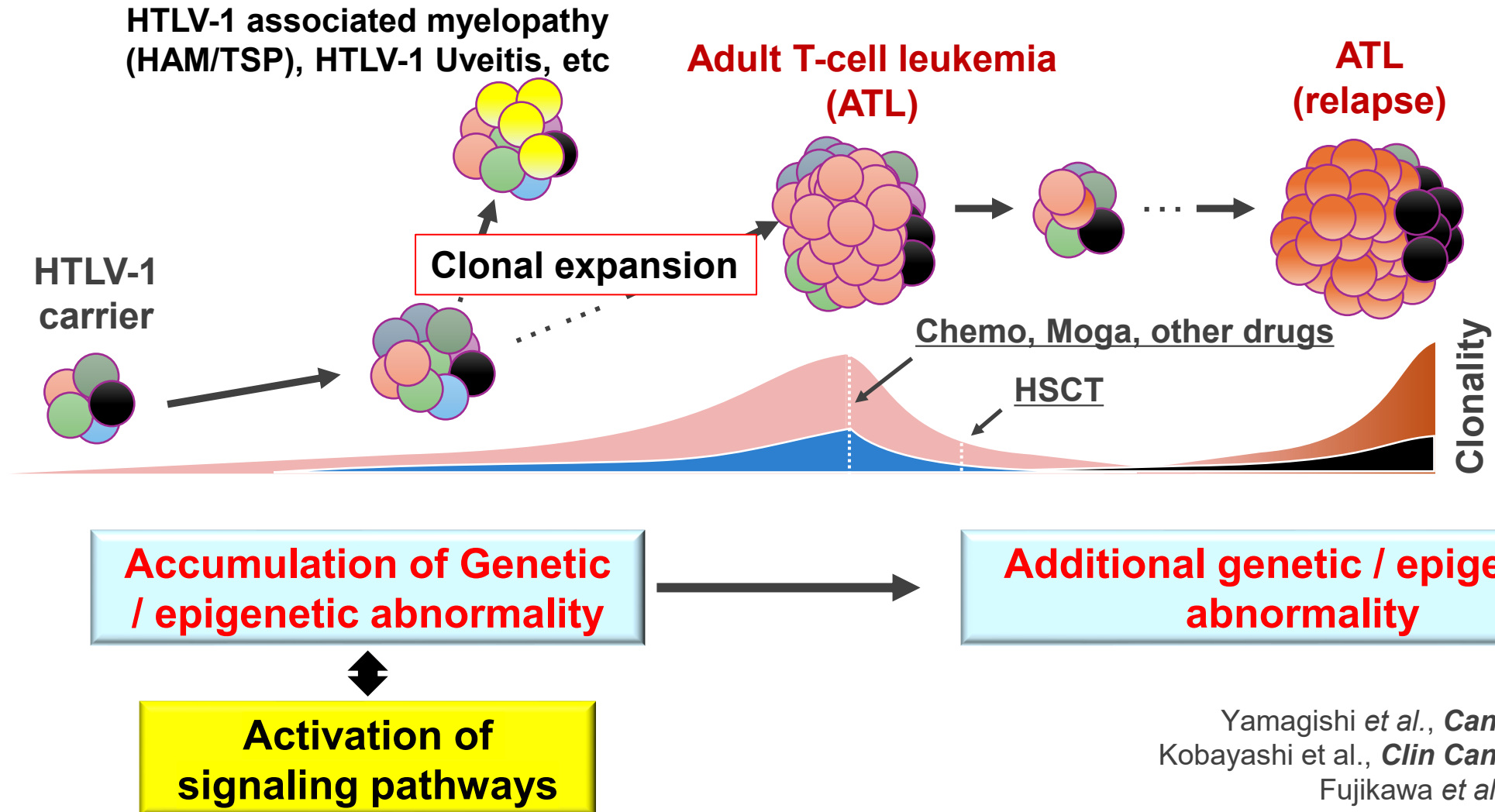
Toshiki Watanabe
St Marianna University, Japan

Targeting Epigenetic and other pathways in ATLL

Toshiki Watanabe, M.D., Ph.D.

**Dept Hematol/Oncol, St Marianna University,
Kawasaki, Japan**

Natural course of HTLV-1 associated diseases



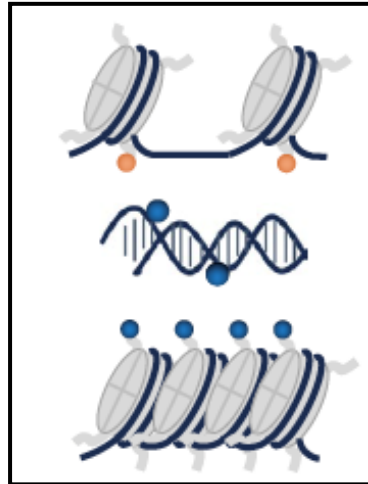
Yamagishi *et al.*, *Cancer Cell*, 2012
Kobayashi *et al.*, *Clin Cancer Res*, 2014
Fujikawa *et al.*, *Blood*, 2016
Yamagishi *et al.*, *Cell Rep*, 2019

Genetic and epigenetic abnormalities in ATL cells

Genetic abnormalities

- TCR/NF- κ B pathway (VAV1, PKCB, REL, et al)
- Signaling pathways (RHOA, NOTCH1, STAT3, et al)
- T-cell trafficking (CCR4, CCR7, GPR183)
- Tumore suppressors (TP53, CDKN2A, POT1)
- Transcription factors (TBL1XR1, GATA3, IKNF2)
- Epigenetic factors (TET2, KDM6A, EP300, ARID2)
- RNA binding (HNRNPA2B1, YTHDF2, CELF2)
- Immune response (PDL-1, HLA-A, HLA-B, CD58, FAS)

Epigenetic alterations



Histone acetylation

Abnormal
enhancer formation

CpG island hyper-
methylation

H3K27m3 accumulation

Oncogene activation

Reduced chromatin
accessibility
Gene inactivation
TSGs

ATL treatment by Targeting Epigenetic Pathways

Histone methylation

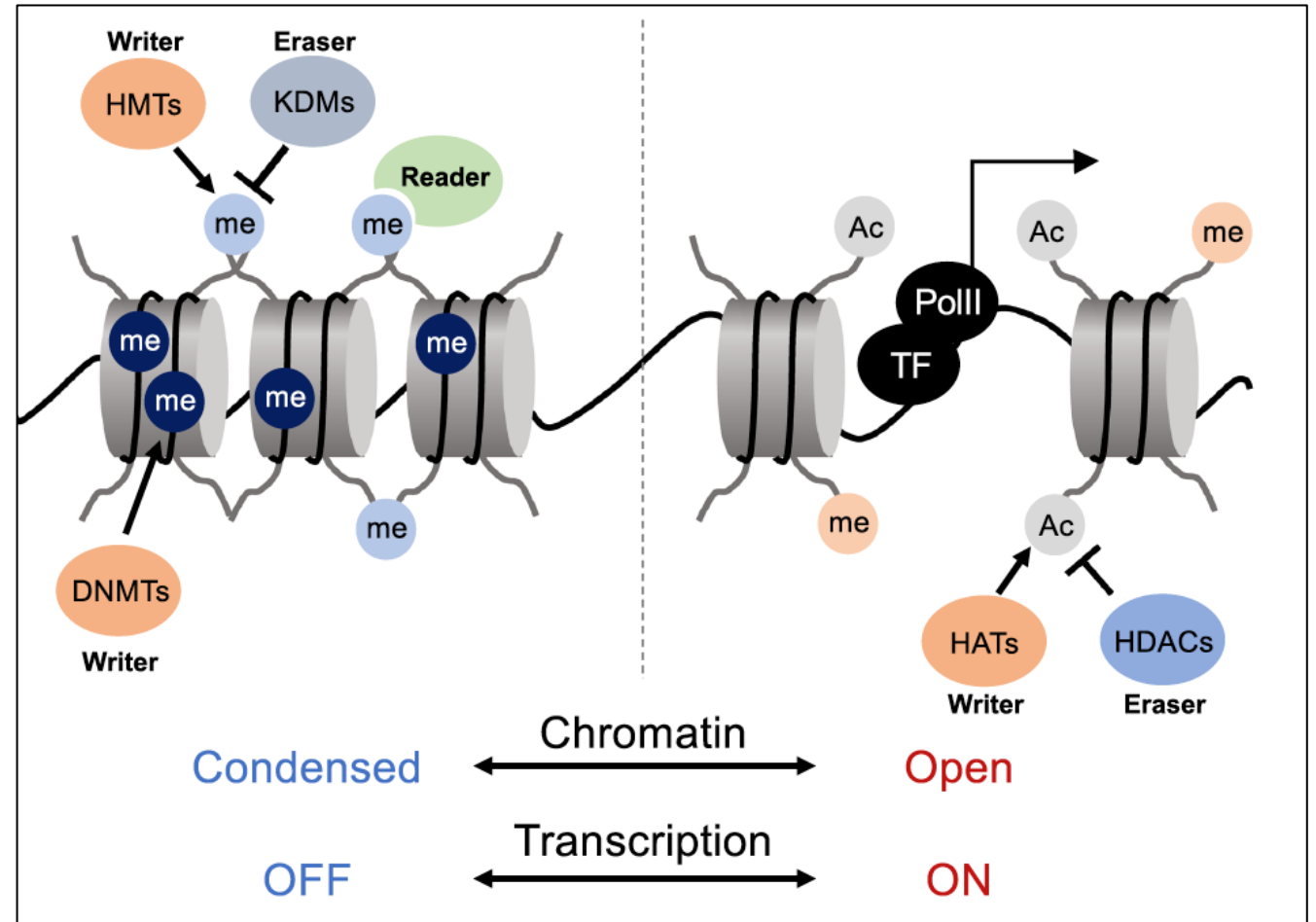
Valemetostat: Phase 2 data
+ clinical data

Histone acetylation

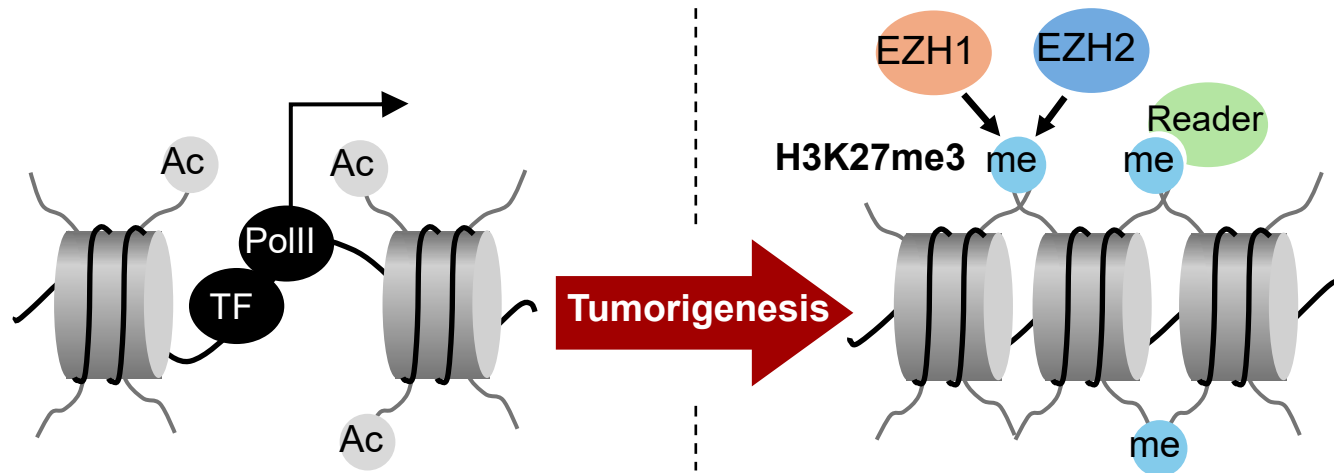
Tucidinostat: Phase 2 data
+ clinical data

DNA methylation

OR-2100: Preclinical studies



Epigenetic regulation by EZH1/2-mediated H3K27me3



Open

ON

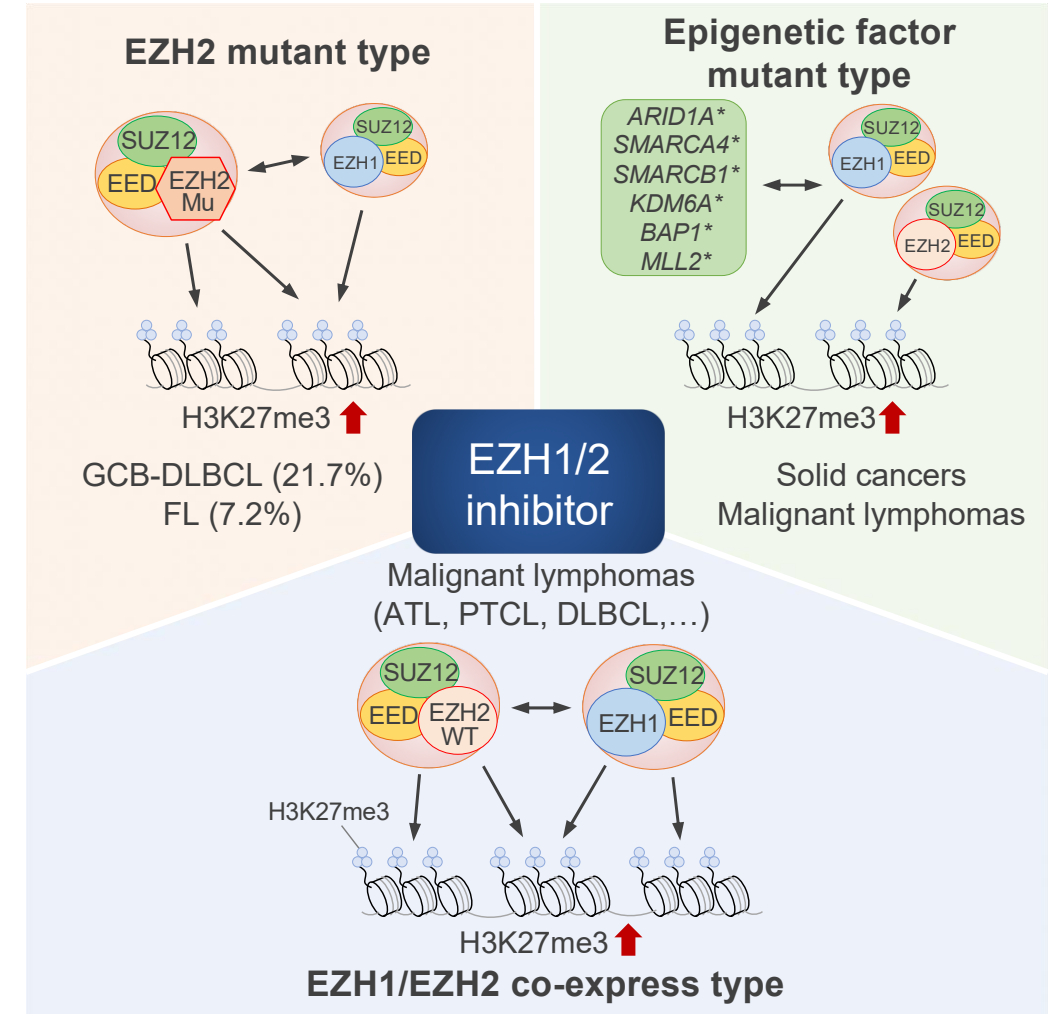
Chromatin

Condensed

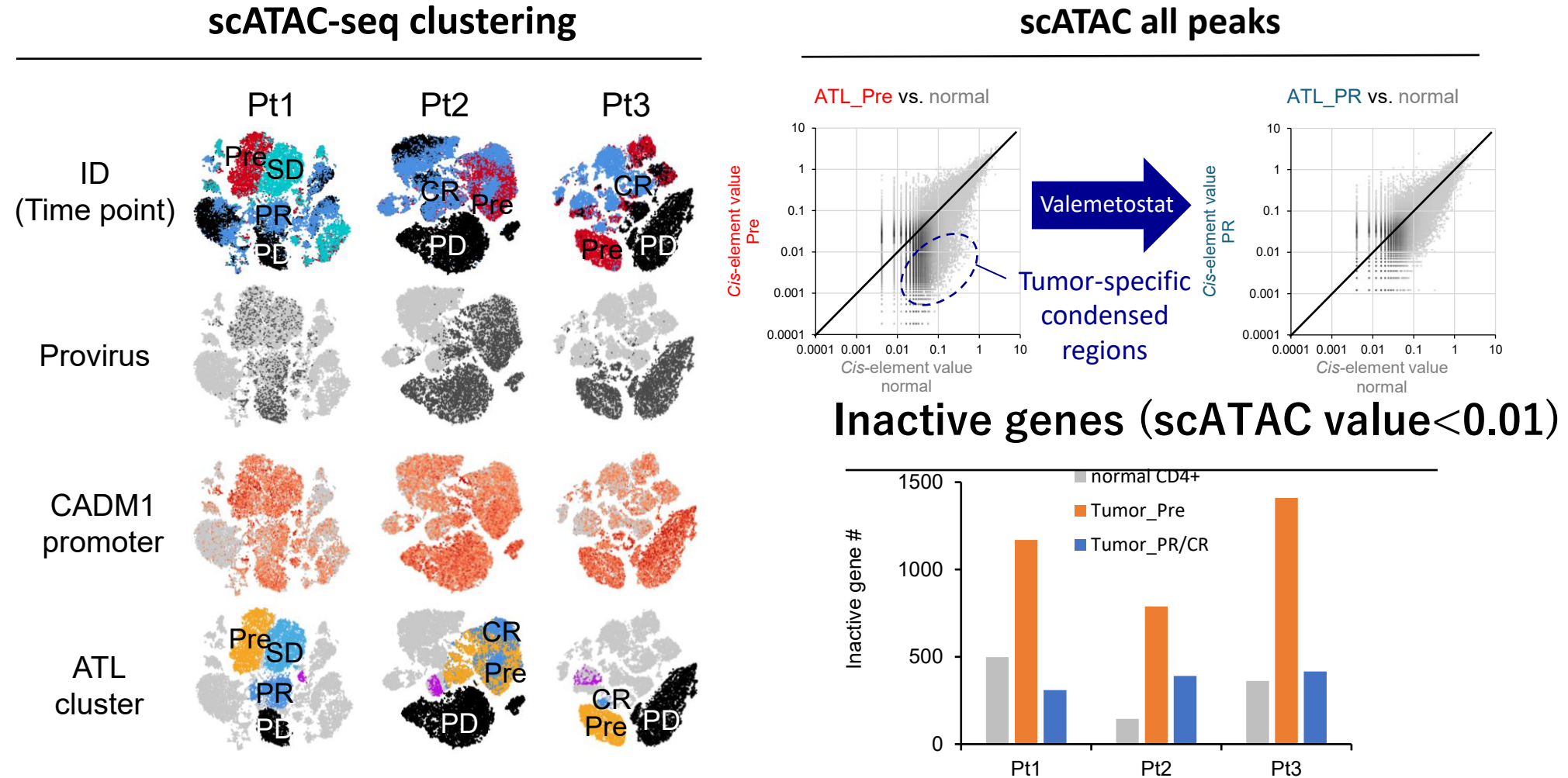
Gene expression

OFF

Yamagishi et al., *Cell Rep.*, 2019
Yamagishi et al., *Int J Hematol*, 2022

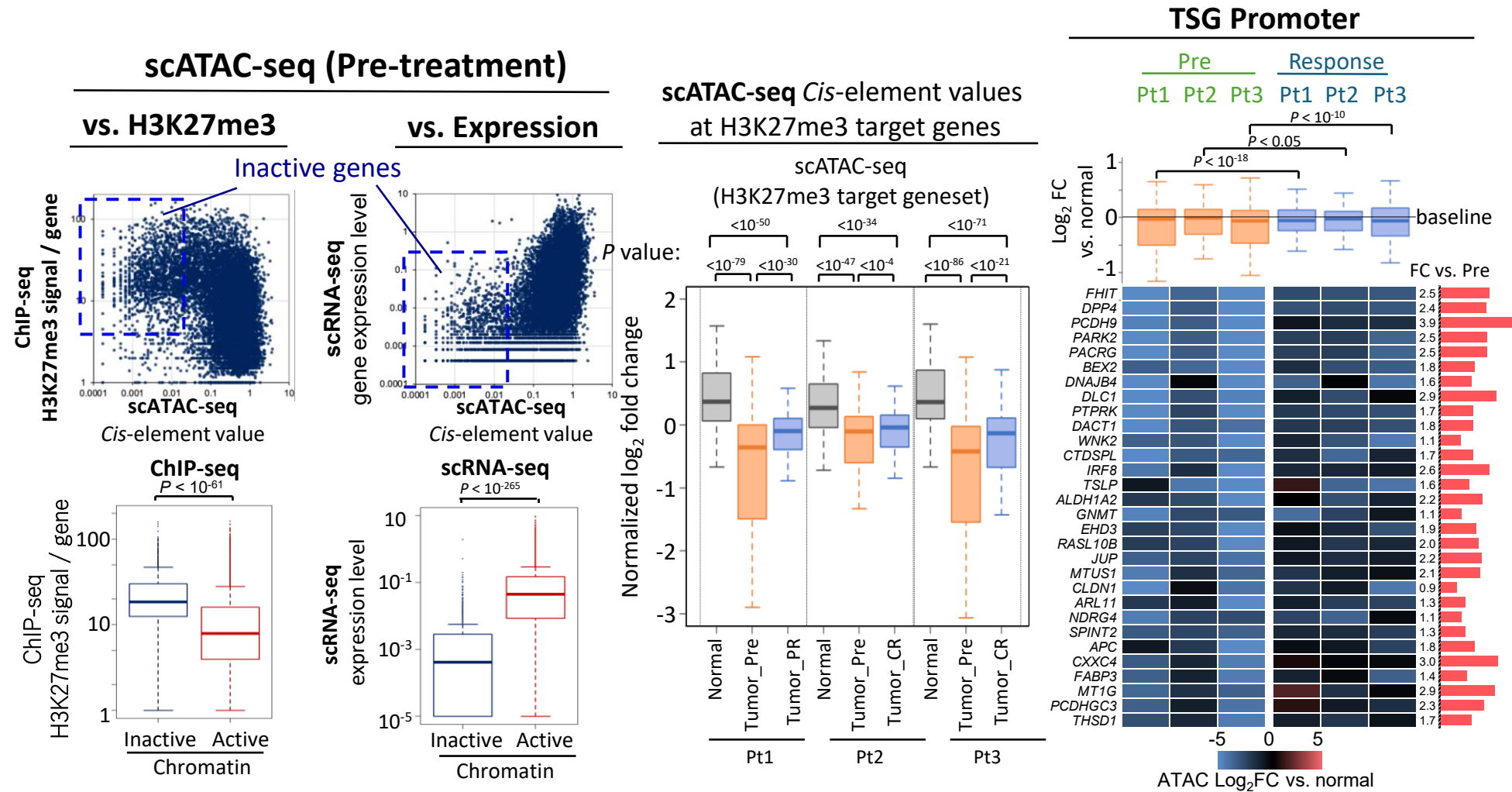


Condensed chromatin and H3K27me³ - Effects of valemetostat



Valemetostat relaxes aggregated chromatin and releases inactivated genes.

Valemetostat reprograms tumor epigenome



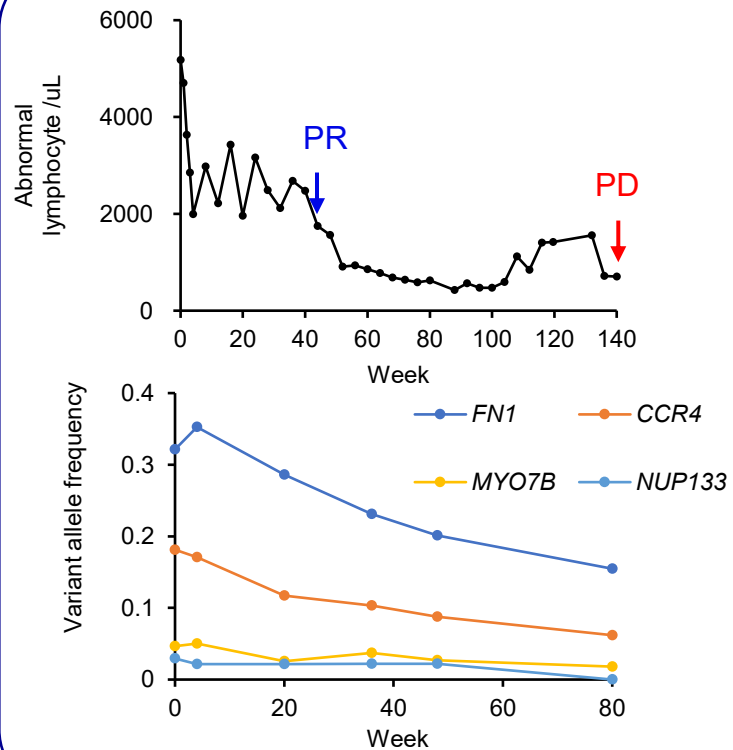
Valemetostat activates H3K27me3-enriched tumor suppressor genes

Clinical and molecular response

J101_Pt1

Best response: PR

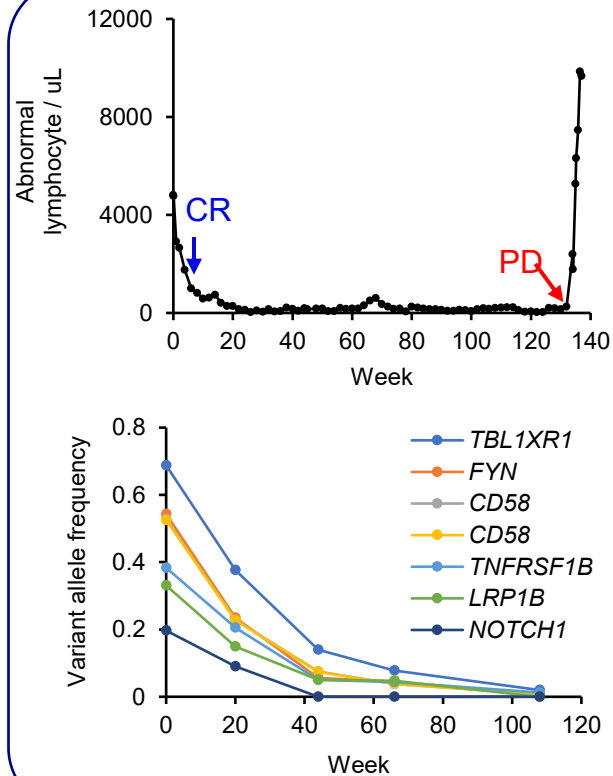
PD at 140 weeks (Cycle 35)



J101_Pt2

Best response: CR

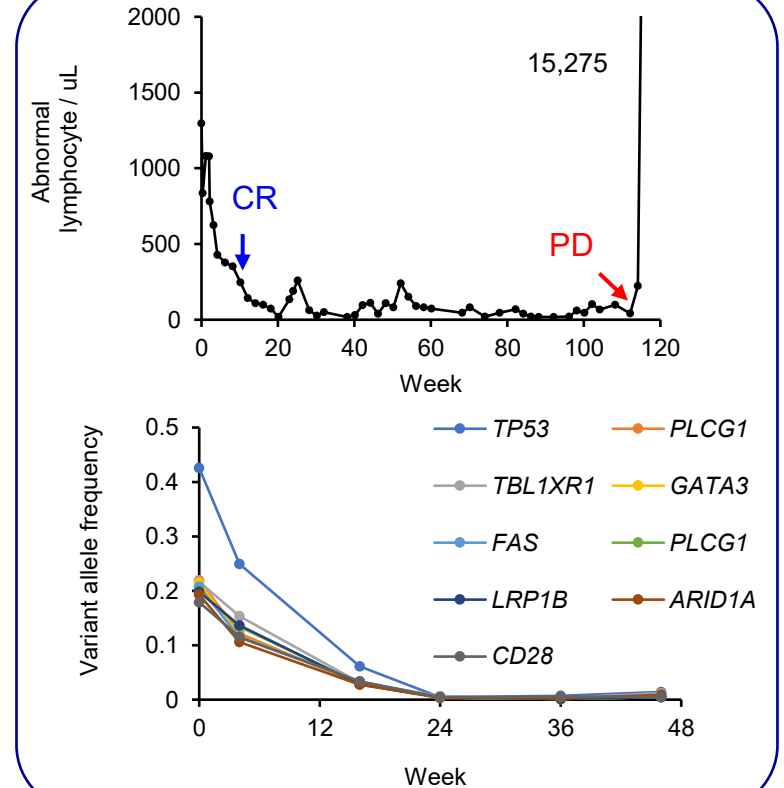
PD at 137 weeks (Cycle 34)



J101_Pt3

Best response: CR

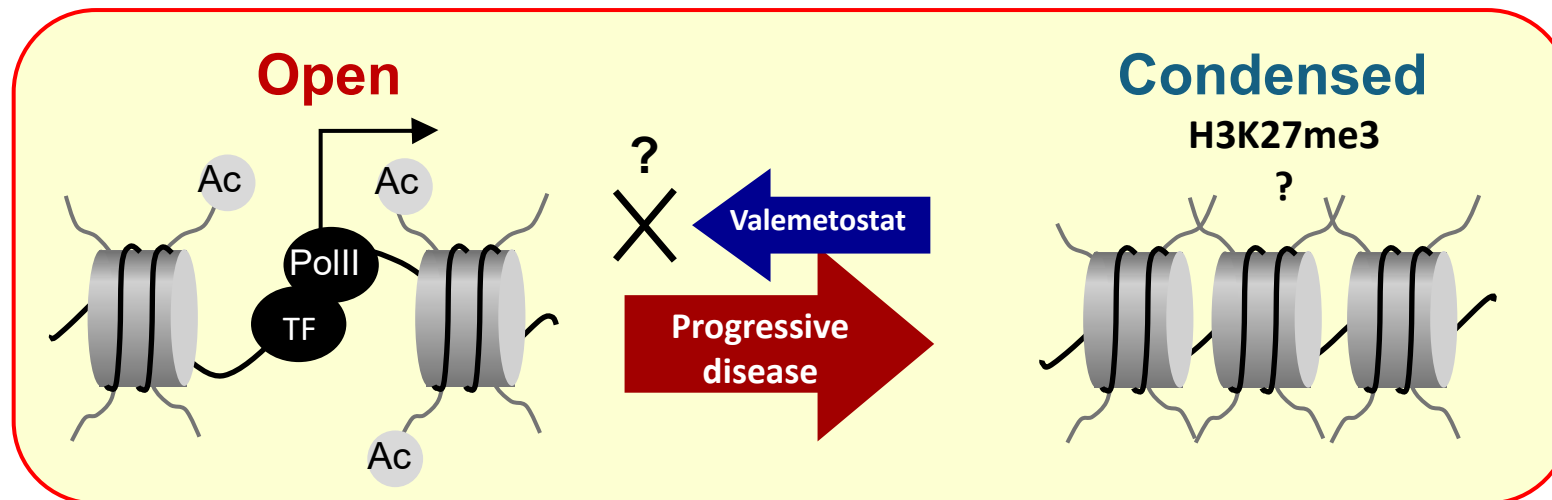
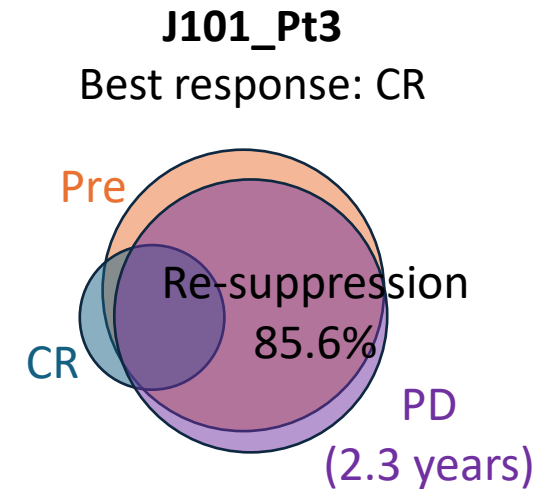
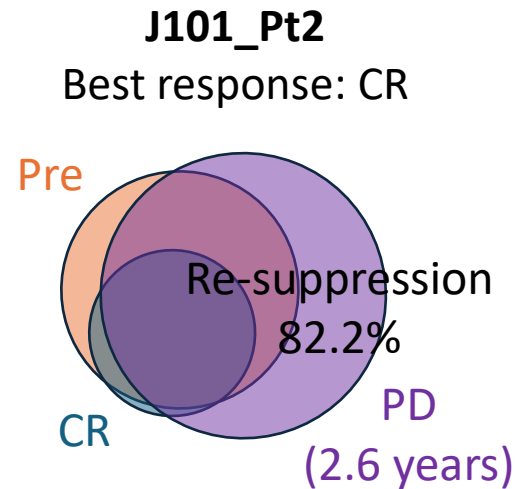
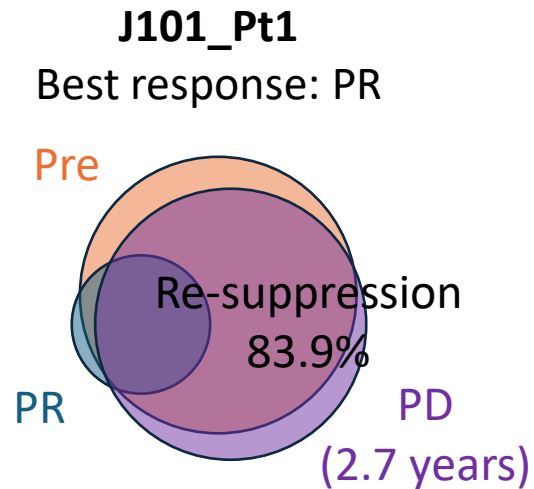
PD at 117 weeks (Cycle 28)



3 cases with CR eventually relapsed

Chromatin re-condensation in progressive disease

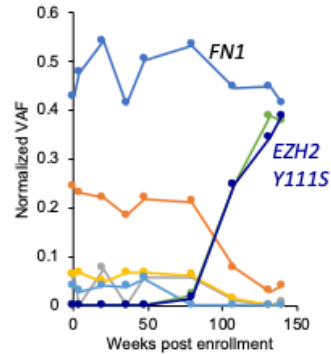
chromatin-condensed inactive genes (scATAC-seq)



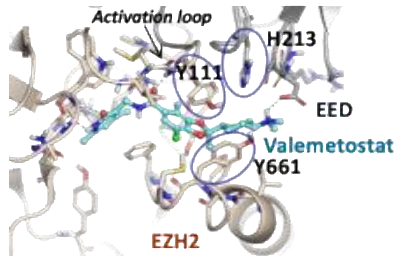
Three resistant mechanisms in relapsed cases

1) *EZH2* Y111 mutation

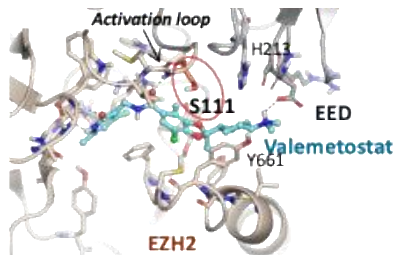
Clonal dynamics (Pt1)
(Normalized by tumor burden)



EZH2 WT (Pre-treatment)

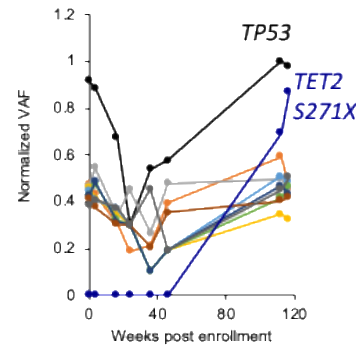


EZH2 Y111S (Valemetostat PD)

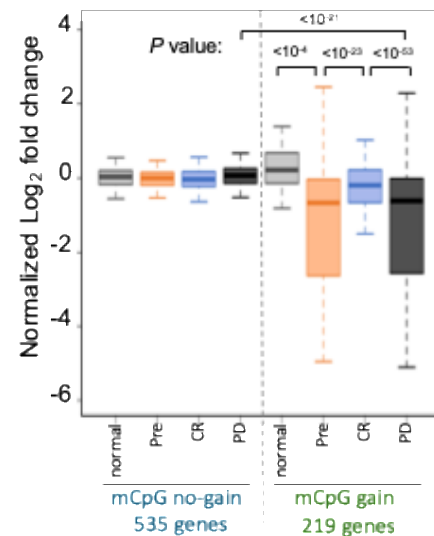


2) *TET2* mutation

Clonal dynamics (Pt3)
(Normalized by tumor burden)

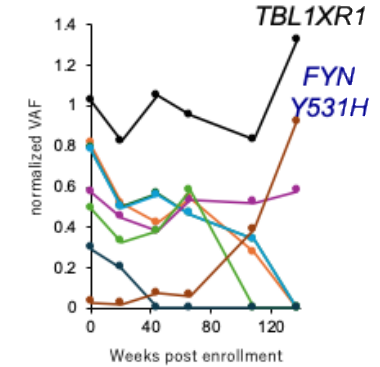


TSG promoter (scATAC-seq)

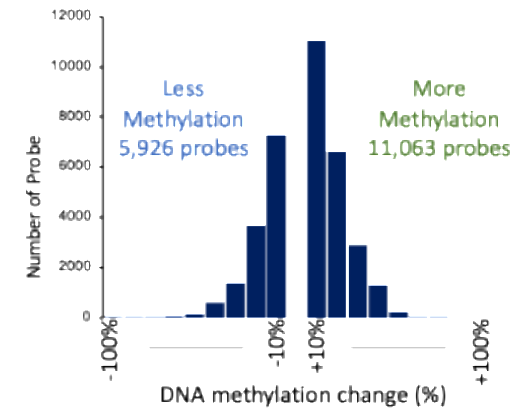


3) DNMT3A overexpression

Clonal dynamics (Pt2)
(Normalized by tumor burden)

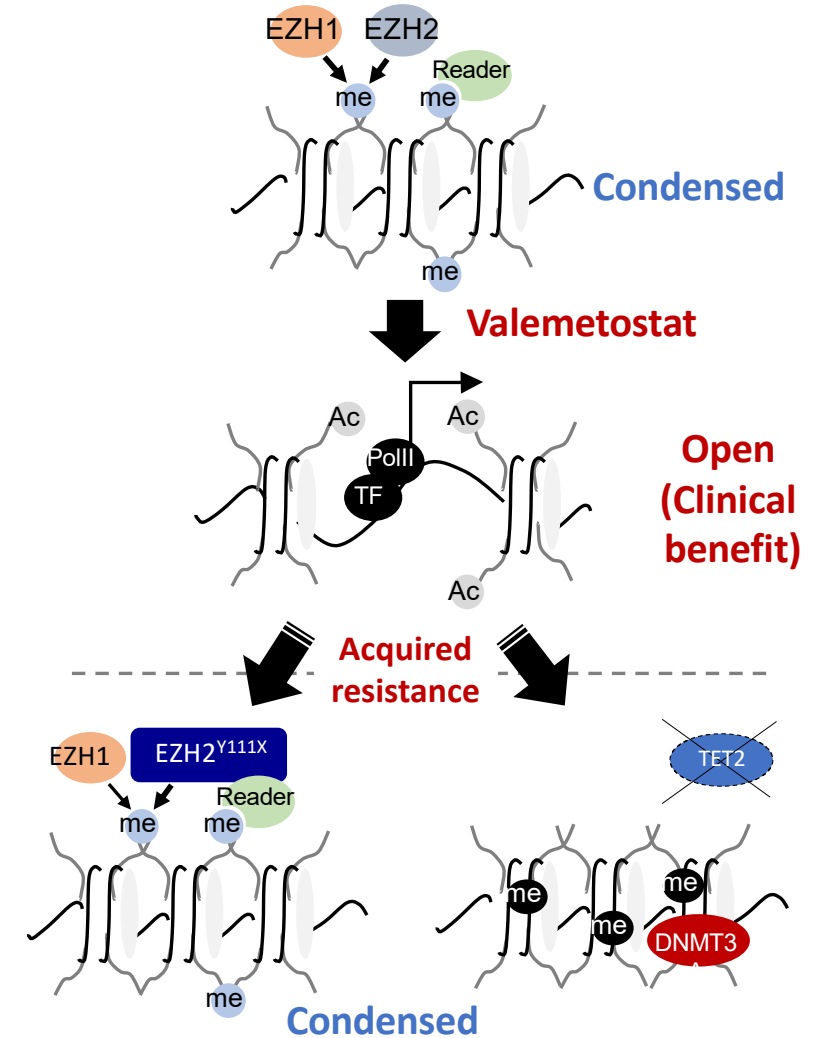
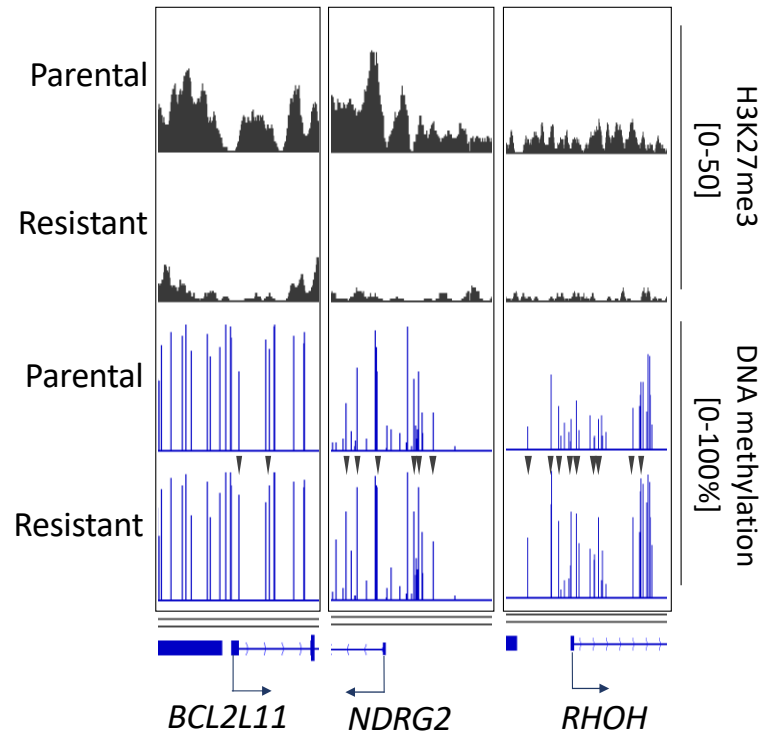
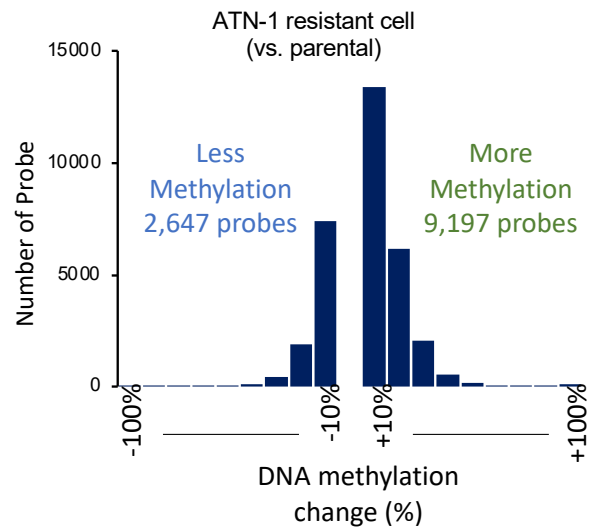
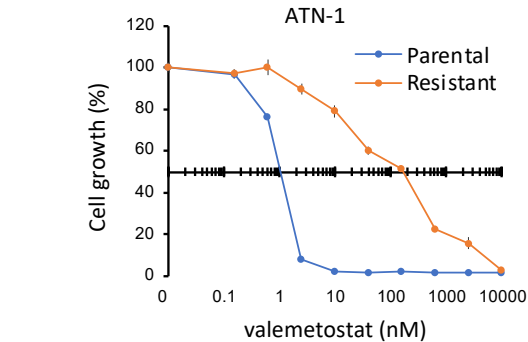


850K probe mCpG array
(PD vs. Pre)



DNA methylation compensates H3K27me3 loss

In vitro resistance model (~2 months exposure)



Summary

➤ Mechanism of Action in patients

- Inhibition of EZH1/2 reduces tumor H3K27me₃.
- Targeting H3K27me₃ releases abnormally condensed chromatin in tumor.
- Upregulation of tumor suppressor genes.

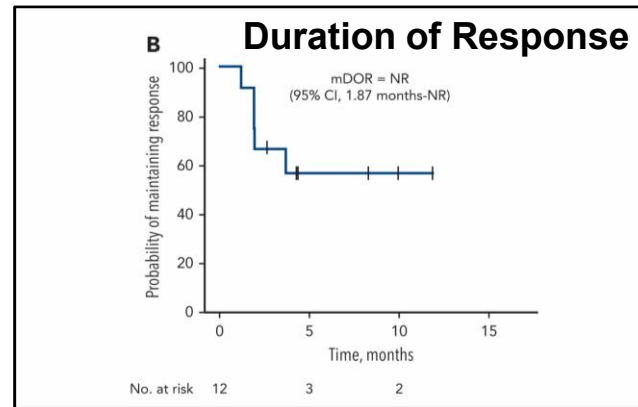
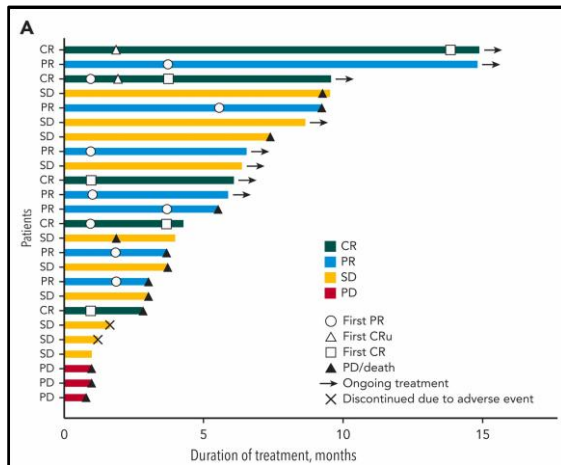
➤ Mechanisms of Resistance in patients

- Three resistant mechanism revealed in Ph2 study for r/r ATL.
 - 1) ***EZH2* Y111 mutation**
 - 2) ***TET2* mutation**
 - 3) **DNMT3A overexpression**

Valemetostat: phase 2 clinical study and real-world data

Phase 2 study

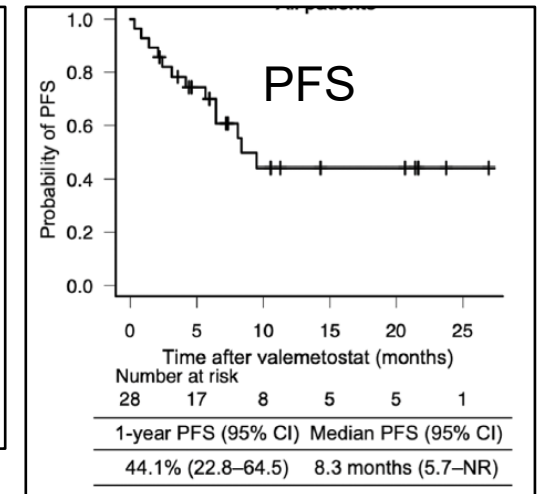
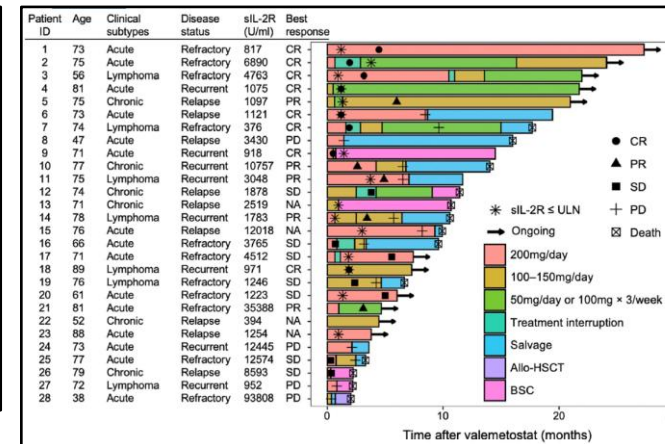
25 patients with R/R aggressive ATL



Overall response rate (ORR) :48.0%
Complete response (CR) rate: 20.0%

Real-world data

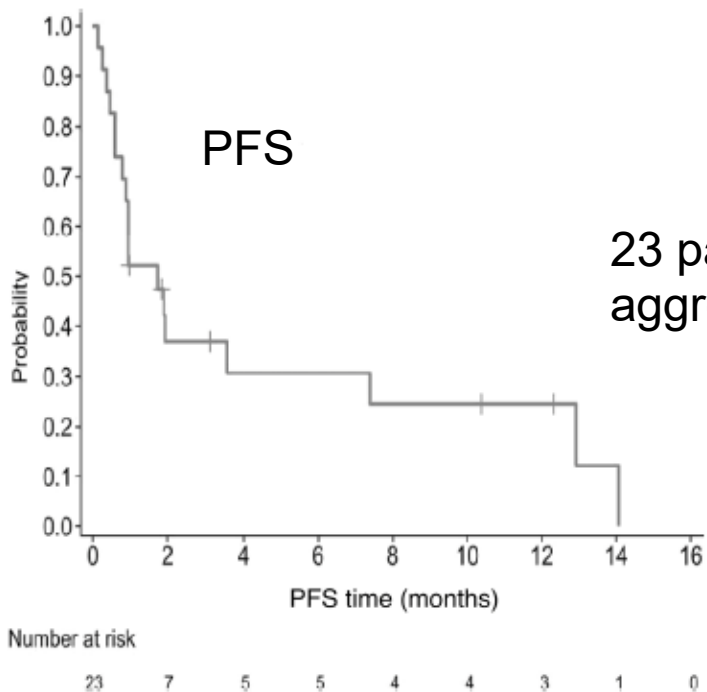
28 patients with R/R aggressive ATL



Overall response rate (ORR): 54.2%
Complete response (CR) rate: 33.3%
Median survival time: 15.8 months
Median progression-free survival (PFS): 8.3 months

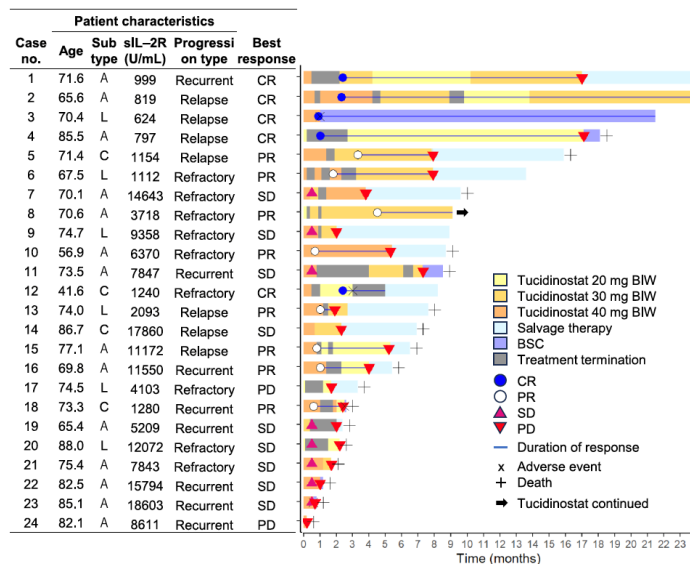
Tucidinostat: phase 2 clinical study and real-world data

Phase 2 study



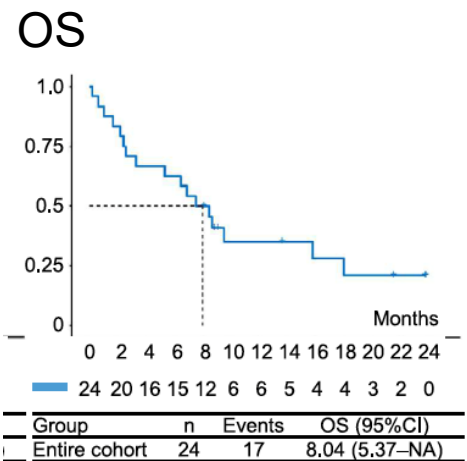
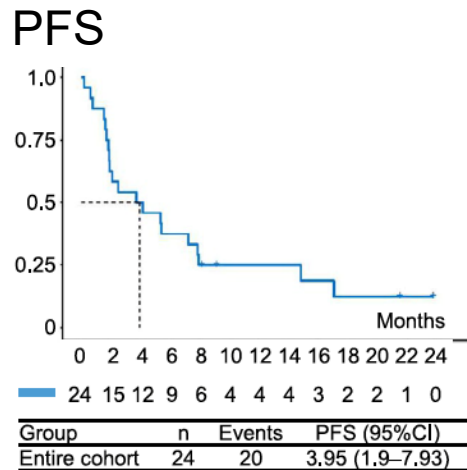
ORR: 30.4%
DCR: 52.2%,
Median PFS: 1.7 months,
Median OS: 7.9 months

Real-world data



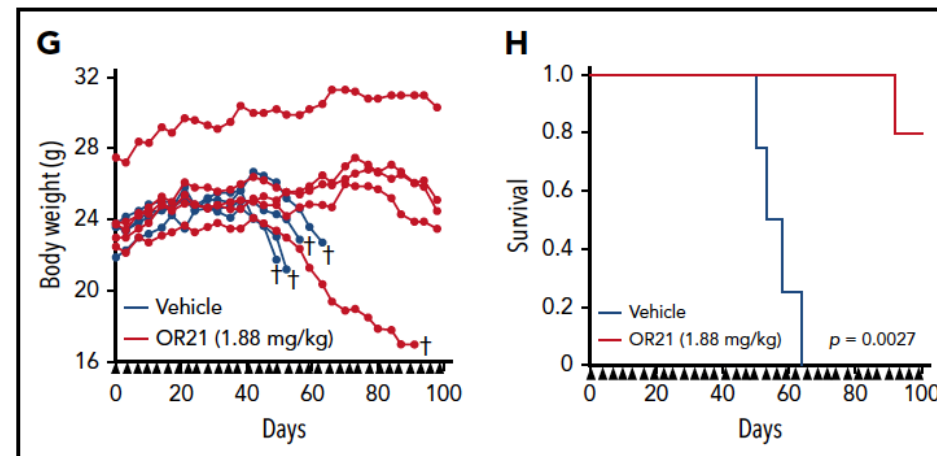
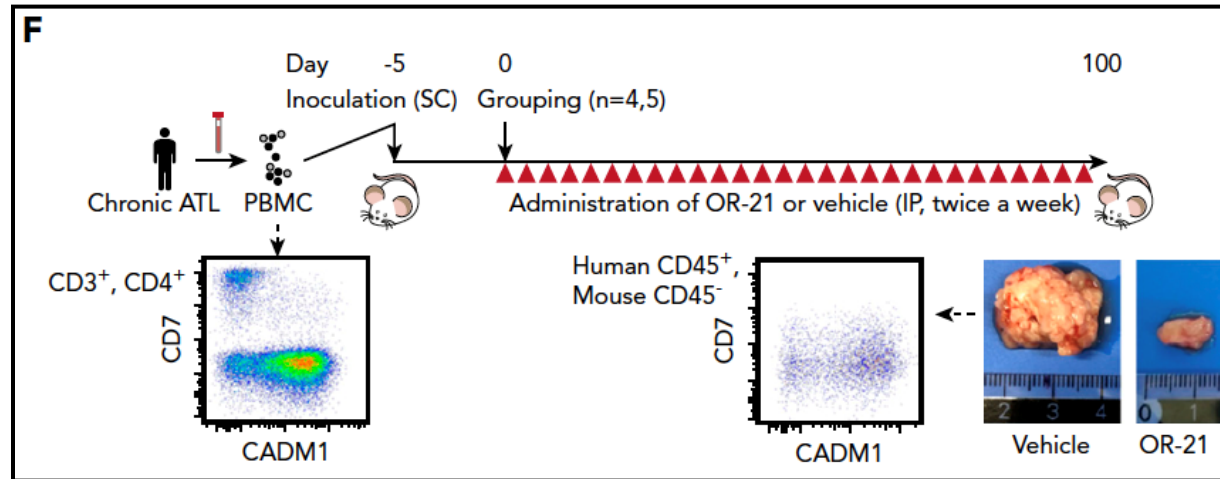
24 patients with R/R aggressive ATL

ORR: 54.2%
DCR: 91.7%,
Median PFS: 3.95 months,
Median OS: 8.04 months



Pre-clinical study with OR-2100 Targeting aberrant DNA hypermethylation of ATL

- HTLV-1 infection specific regional DNA hypermethylation reflects disease development and progression of adult T-cell leukemia/lymphoma
- OR-2100, a novel decitabine prodrug with enhanced oral bioavailability, exerts potent anti-ATL activity through DNA hypomethylation.

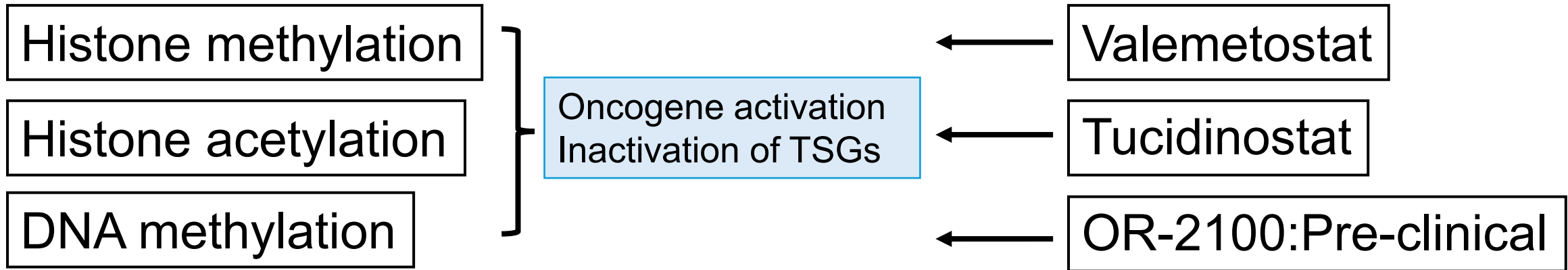


Results of xenograft model

Clinical study is in preparation.

Watanabe et al., Blood.
2020;136(7):871-884

Epigenetic Abnormalities leading to tumorigenesis



Genetic Abnormalities leading to signaling activation

Activation of

- NF- κ B pathway
- JAK-STAT pathway
- PI3K-AKT-mTOR pathway

Cell growth and
resistance
to apoptosis



No specific drugs
In clinical use



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

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

Adult T-cell leukemia/lymphoma in 2026, and hopes for prevention

Lucy Cook
Imperial College Healthcare Nhs Trust, London, UK

Adult T-cell leukaemia/lymphoma in 2026 - Hopes for prevention

Dr Lucy Cook PhD MB BS, Consultant Haemato-oncologist

Haematology and HTLV departments, Imperial College Healthcare NHS Trust

Shimoyama/WHO classification

	← "AGGRESSIVE" →		← "INDOLENT" →		
	Acute ^ (Leukemic)	ATL Lymphoma	Chronic Unfav*	Chronic Fav	Smoldering
Anti-HTLV-1 Ab	+	+	+	+	+
Circulating ATL cells	+	-	+	+	+
Lymphocytosis (ALC > 4000)	Variable	No	Yes	Yes	No
Circulating abnormal lymphocytes	Variable	≤1%	Variable	Variable	≥5% or <5% if ATL lesion(s) in the skin and/or lung
LDH	Variable	Variable	<2× ULN, or *	normal	≤1.5 ULN
Calcium level	Variable	Variable	<11.0	normal	normal
Rash	Variable	Variable	Variable	Variable	Variable
Lymphadenopathy	Variable	>1.5 cm	Variable	Variable	No
Organomegaly	Variable	Variable	Mild	Mild	No
BUN			>ULN	NL	
Albumin			<LLN	NL	
CNS involvement	+/-	+/-	No	No	No
Bone lesions	+/-	+/-	No	No	No
Ascites	+/-	+/-	No	No	No
Pleural effusion	+/-	+/-	No	No	No
GI tract	+/-	+/-	No	No	No



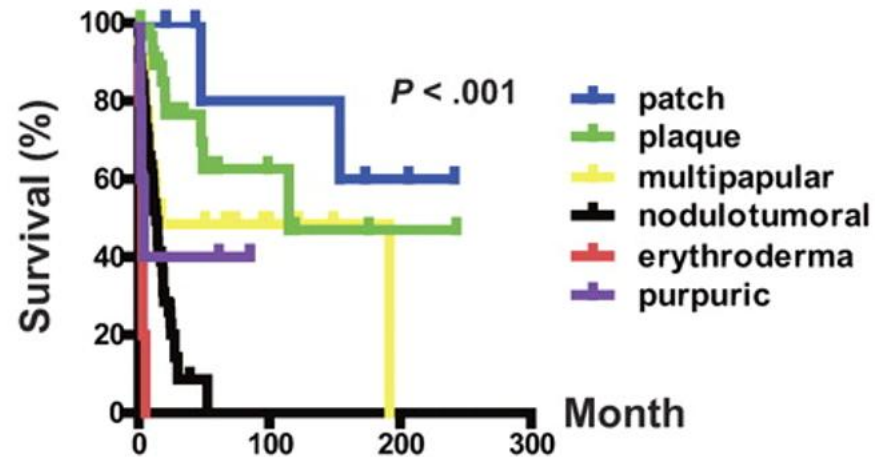
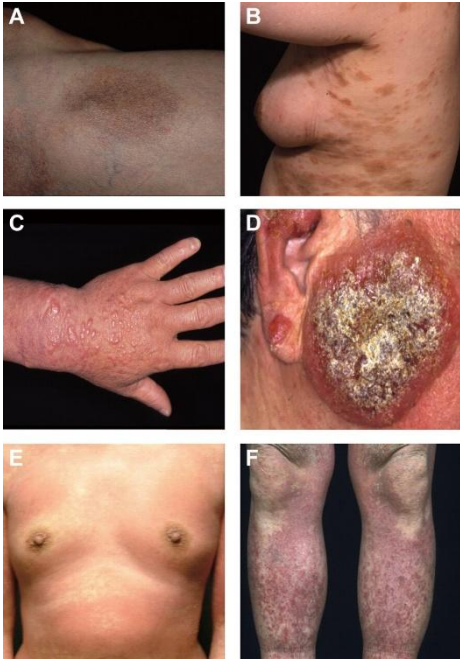
Needs updating: Not biologically driven; based on blood film morphology;

More recent entities not recognised (e.g primary cutaneous)

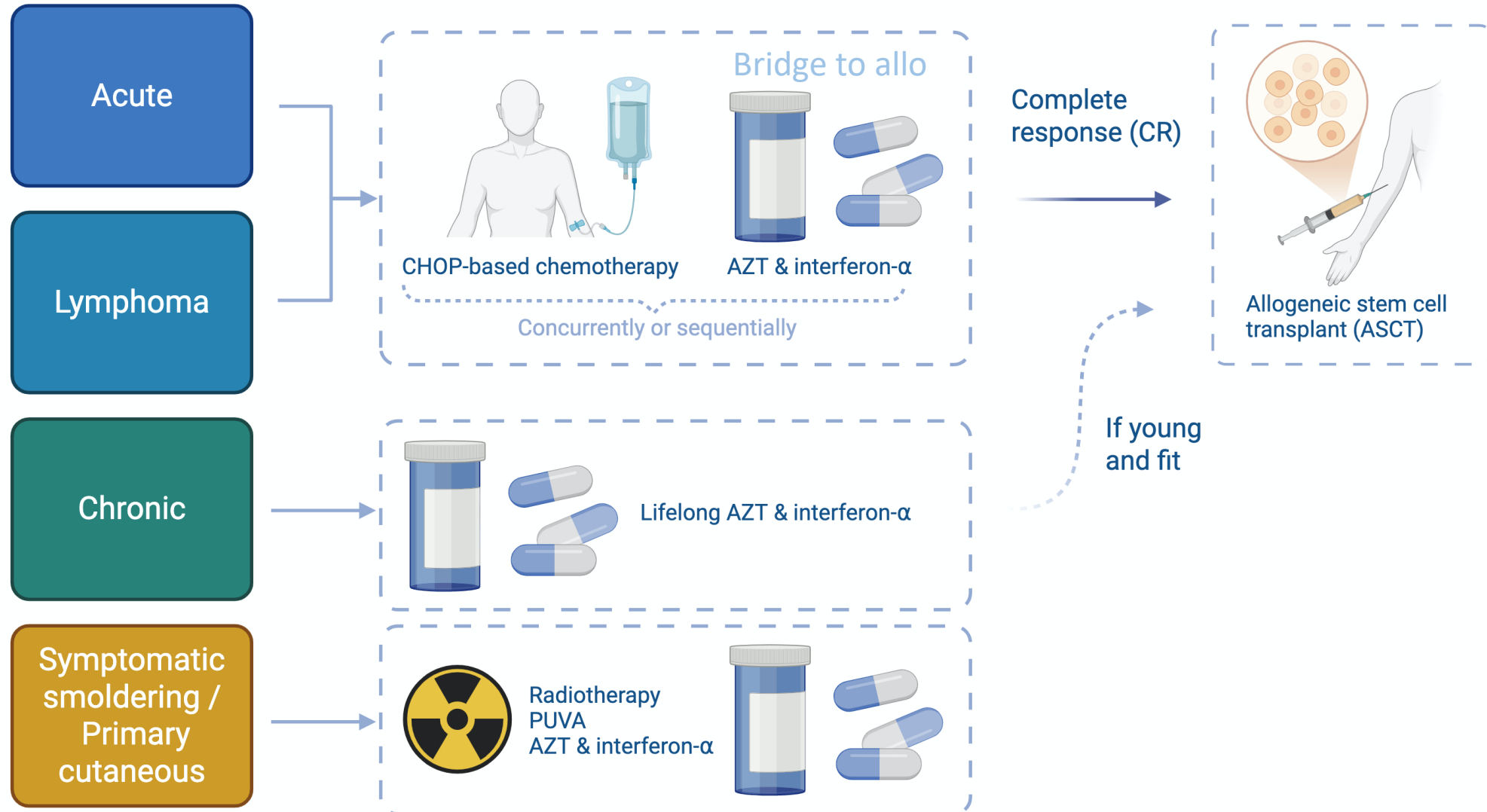
Doesn't distinguish symptomatic v asymptomatic smoldering

-Some asymptomatic smoldering will be high load carriers, others are 'high risk' carriers

Skin disease – 50% cases, very frequent chronic/smoldering

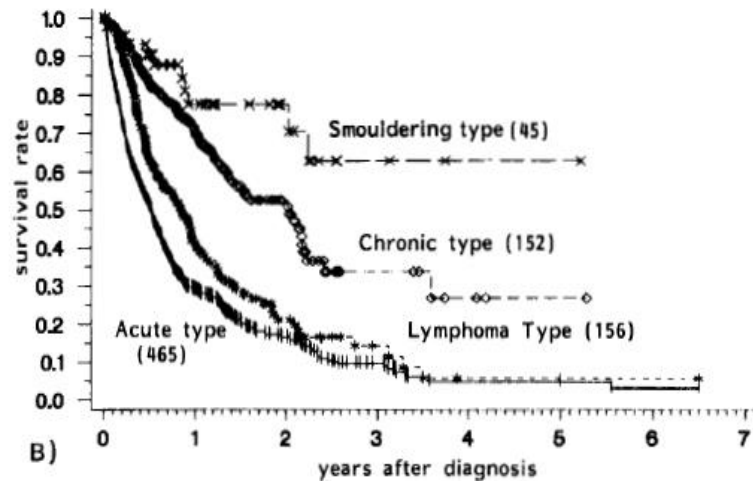


Current Treatment approach: no licensed drugs

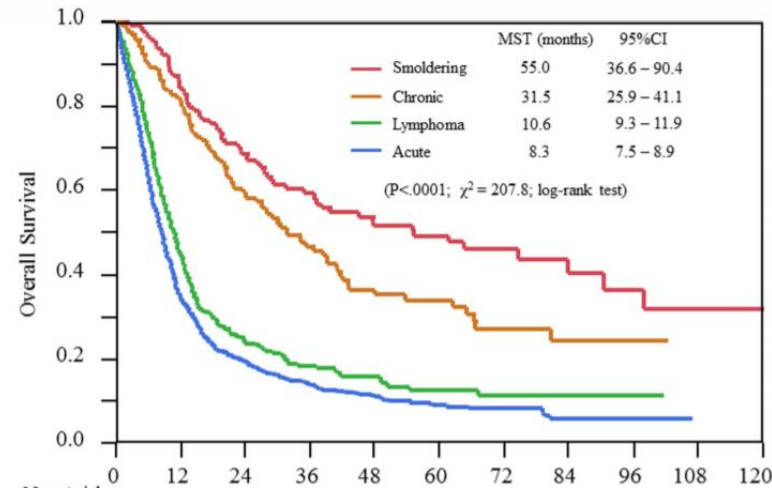


Overall survival not improved by chemotherapy only based strategies in ~40 years since ATL first described

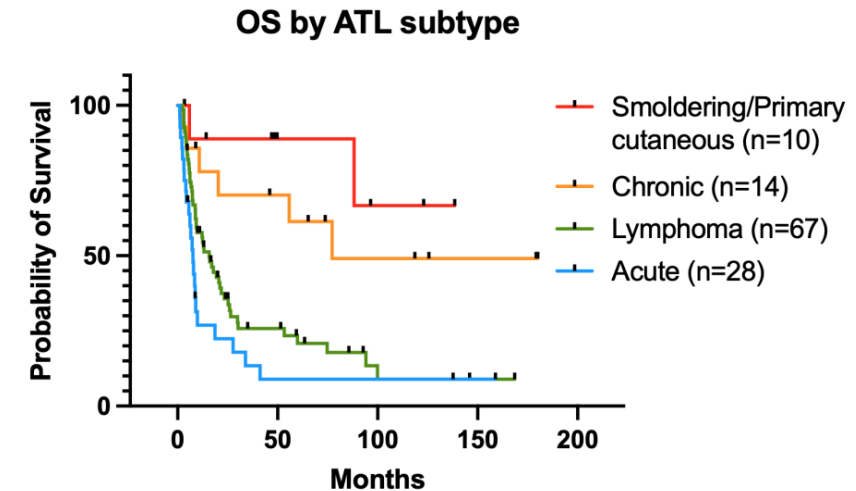
Shimoyama et al, BJH 1991



Katsuya et al, Blood 2015



Imperial, unpublished 2026



Various cohorts-median OS aggressive 8-10 months

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%

Intensification doesn't improve OS

Overall Survival of ATL Pts in JCOG 9801

Tsukasaki K, Tobinai K, et al.: J Clin Oncol 2007;25:5458-64

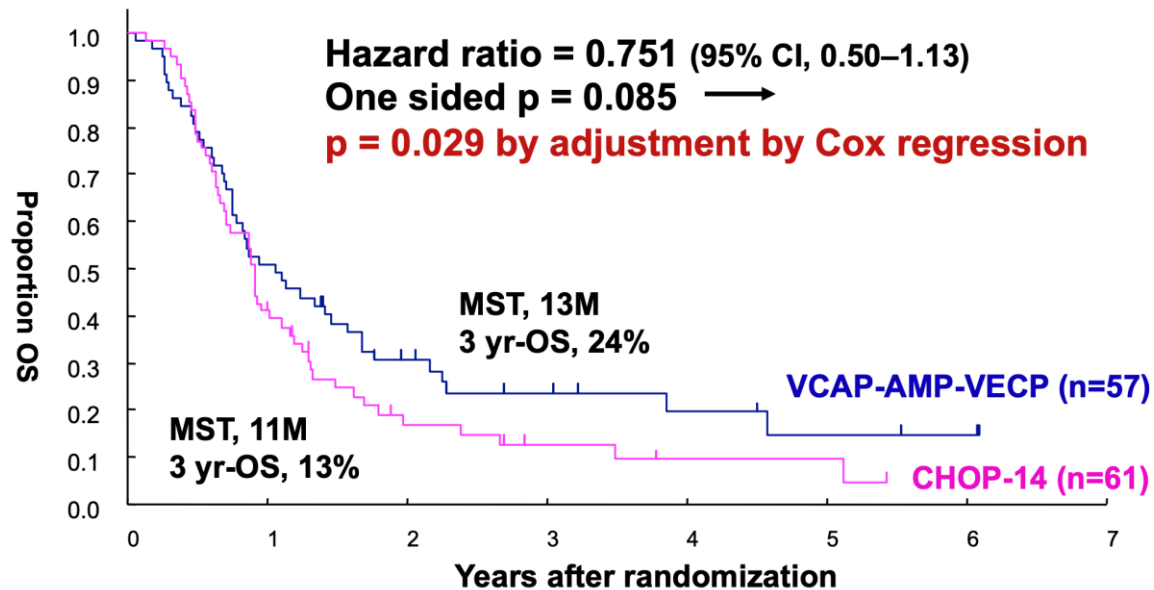


Table 2. Japan Clinical Oncology Group Trials for ATL

Study	N	% CR	MST (mo)	% OS
JCOG8101	54	28	7.5	8 (4 yr)
JCOG8701	43	42	8.0	12 (4 yr)
JCOG9109	60	28	7.4	16 (2 yr)
JCOG9303	93	35	13	31 (2 yr)
JCOG9801	118	32	11	24 (2 yr)

Abbreviations: CR, complete response; JCOG, Japan Clinical Oncology Group; MST, median survival time; OS, overall survival.

VCAP-AMP-VECP (highly intensive regimen): Standard in Japan – **benefit only seen <55 yrs age**, not 56-70 yrs
CHOP14 (or similar intensive regimens), DA EPOCH, hyperCVAD: standard outside Japan

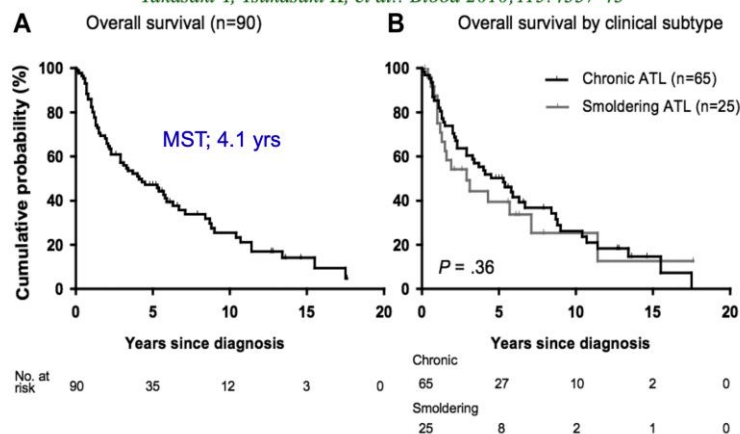
Indolent disease is not so indolent: AZT/IFN?

Bazarbachi A, et al.: J Clin Oncol 2010

UK single centre (unpublished 2025)

Long-term Follow-up Study of Indolent ATL in Japan

Takasaki Y, Tsukasaki K, et al.: Blood 2010;115:4337-43

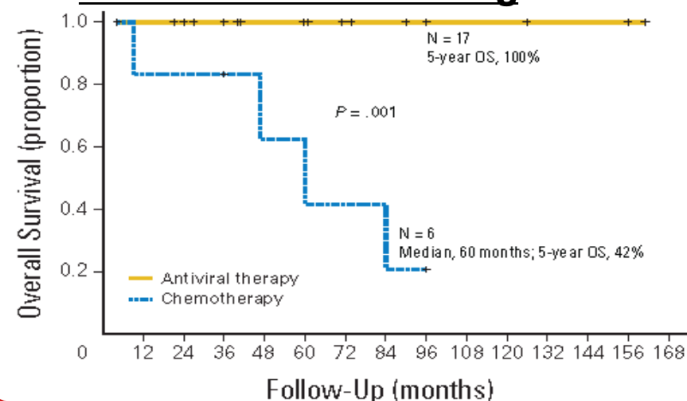


Active monitoring- MST 4.1 years

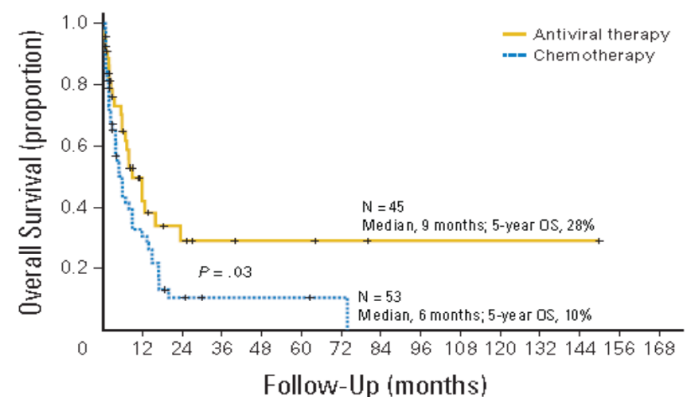
No plateau in curve

Early & fatal transformations

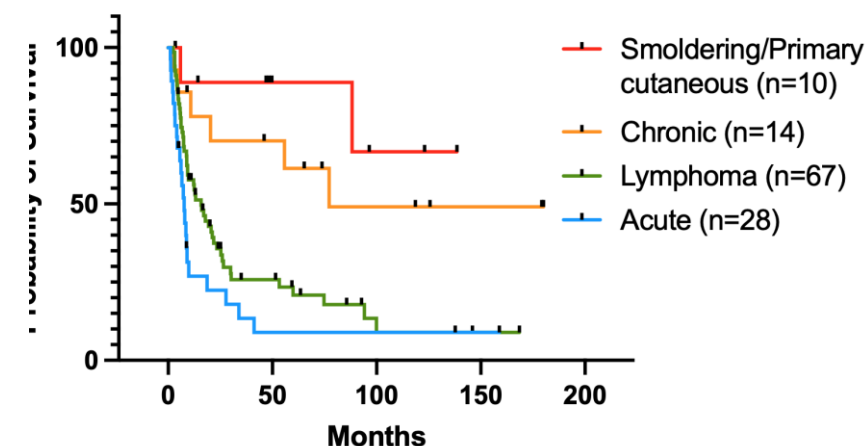
A Chronic and smoldering



C Acute



OS by ATL subtype



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

Smoldering mOS not reached,
2-year OS 88.9%

Challenges and causes of death: progressive disease

1. **CNS progression:** 1 yr cumulative incidence ~12 %
 1. Observed at presentation, during treatment, and synchronous or isolated to systemic disease.
 2. Leukemic disease higher risk (17.8% acute, 1.8% lymphoma, 16% chronic)

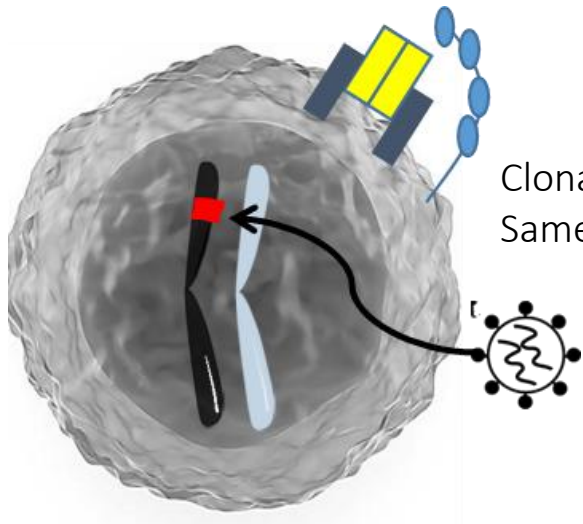
CNS IPI – did not predict, **ATL IPI** – did not predict

What is best standard of care for prophylaxis?

2. Opportunistic infection
Strongyloides coinfection, Aspergillus, candida, Pneumocystis etc, making treatment challenging.

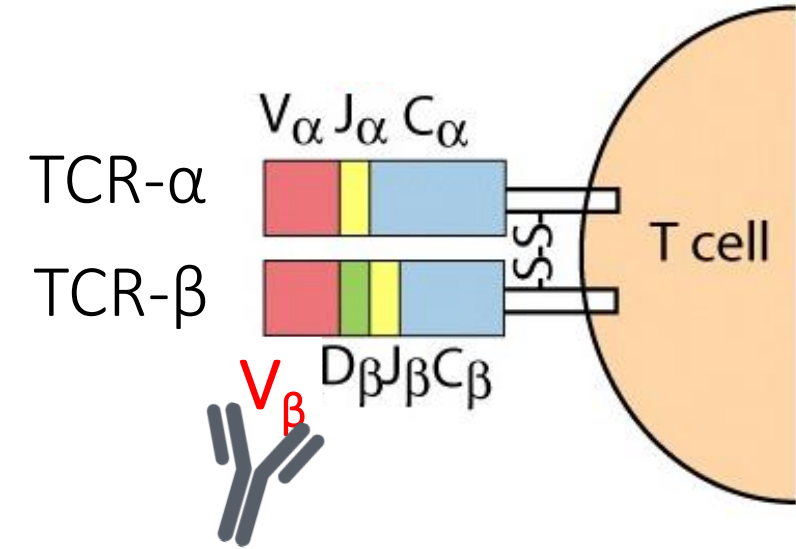
ATL can be predicted using clonality in asymptomatic carriers?

“OCI-flow” panel (UK)



Clonal HTLV cells – daughters with Same insertion site & TCRvB

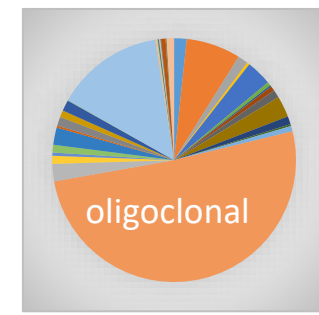
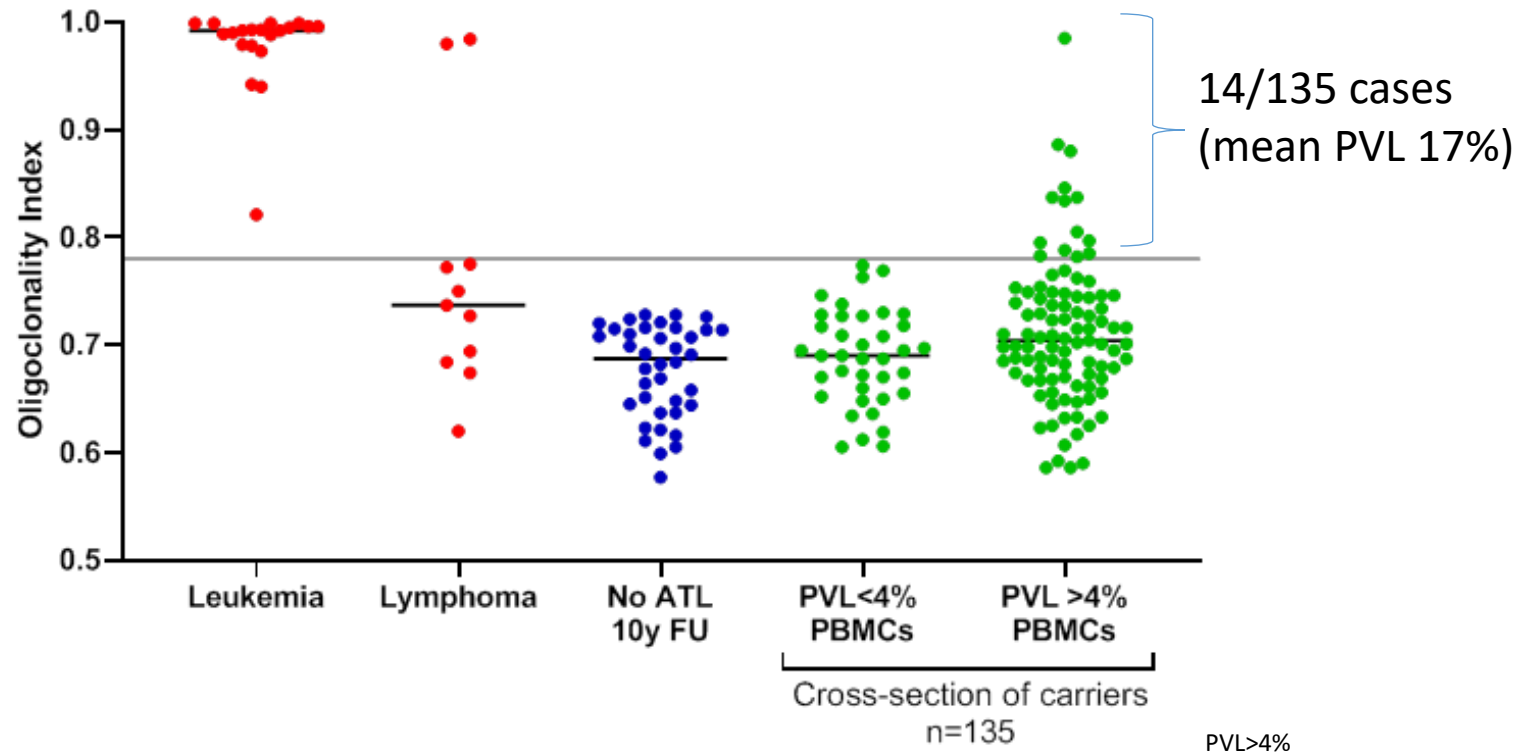
ATL-like clone quantified with flow score



Three main steps....

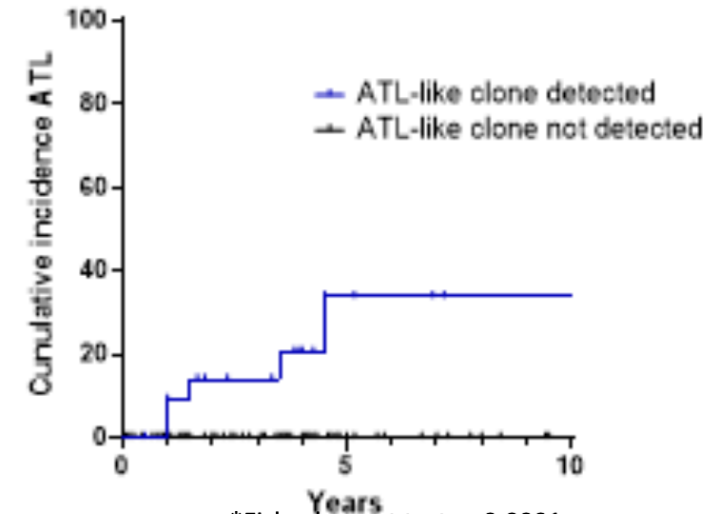
1. Identify infected cells: **CD4+, CCR4+/CADM1+ CD26- T cells**
2. Quantify cells that bind 24 TCRV β chain subunits
3. Evaluate whether one TCRV β subunit is present at a frequency that is higher than expected by chance
4. Flow score >0.77, and/or infected clone with TCRvB >2%

1. Early intervention?



= OCI flow score > 0.770 threshold
(Gini index)
ATL-like clonality

Cumulative incidence



*Fisher's exact test $p < 0.0001$
vs 'clone not detected' group, two tailed

Can we intervene?

- 43 yr old male, referred by UK BTS (blood service) in 2013
- Family history ATL (father died in 6th decade)

No other significant medical history

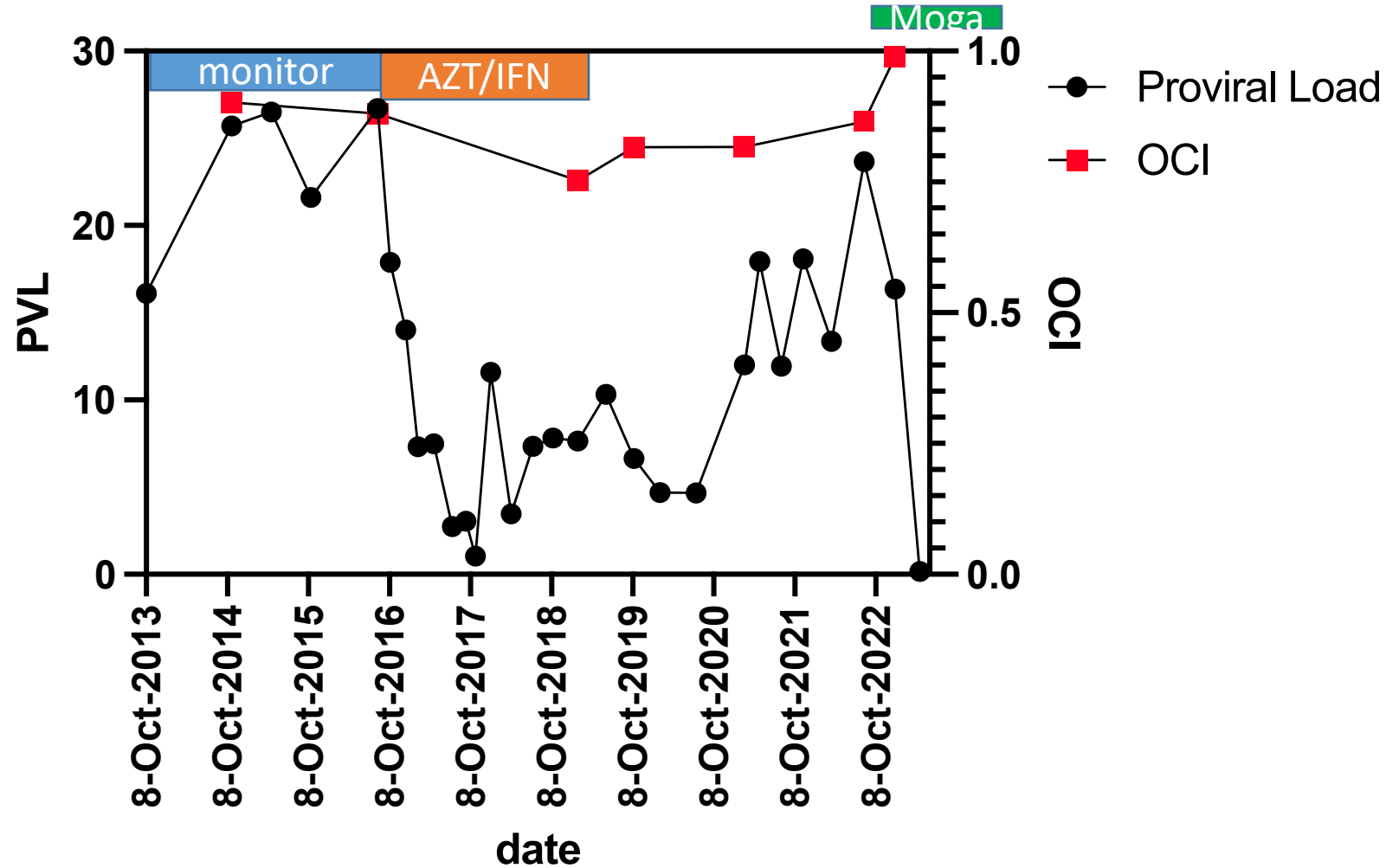
2016:

OCI flow assay being developed, OCI flow score 0.88

CT scan – no occult lymph nodes; normal FBC, normal CD4+, LDH, well

Early intervention might change the risk of clinical progression?

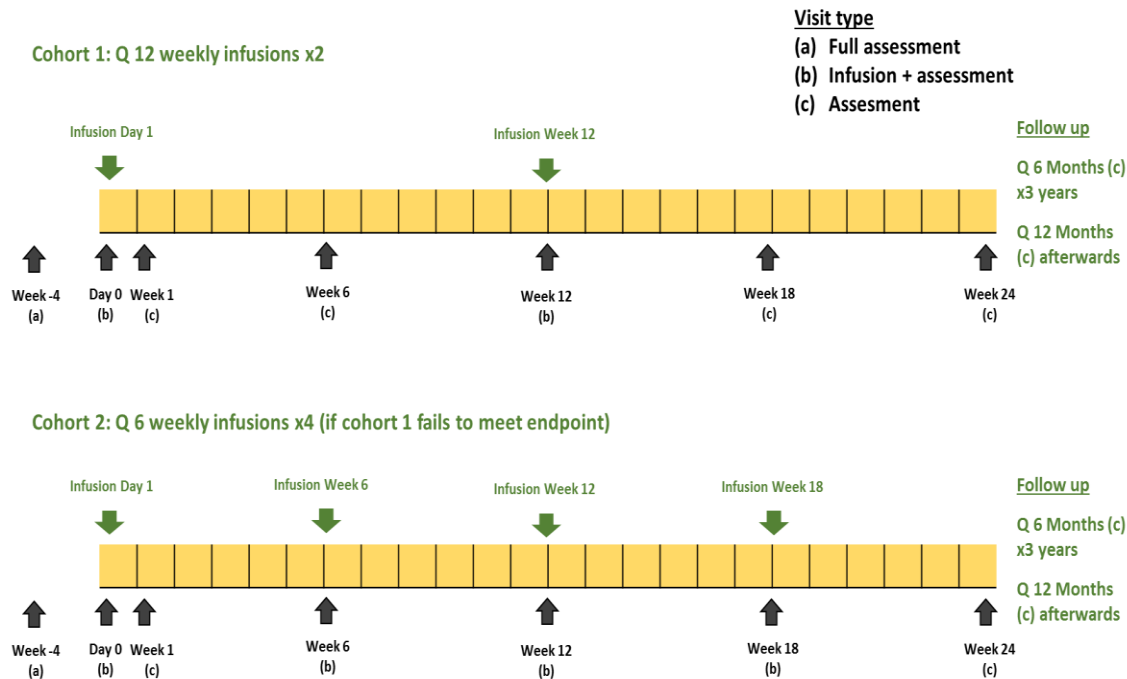
PVL and OCI-flow score respond to treatment



A Study of Mogamulizumab to Prevent Adult T-cell Leukemia/Lymphoma in People With HTLV-1. NCT06698003

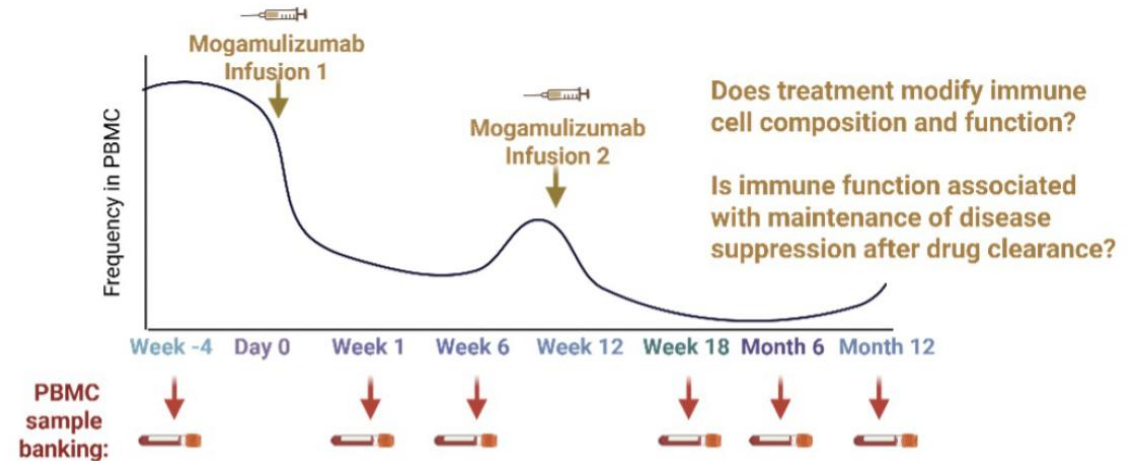
Collaborative study MSKCC/Imperial

2 dosing cohorts



Plenty of exploratory work!

Anticipated impact on frequency of Premalignant clone /HTLV-infected cells



Thoughts and conclusions

- Outcomes remain poor in 2026, high rates of **primary refractoriness** to chemotherapy and **relapse**. CNS disease remains a challenge.
- **Novel first line treatment approaches** need to be explored urgently.
- We can find a subgroup at ultra-high risk (35% in 5 years), and aim to refine this to include molecular or epidemiological: could determine appetite for intervention
 - ATL risk can be prevented by screening for HTLV-1 and public health measures
 - ATL risk may be reduced by risk stratification of carriers, and early intervention

Thank you



National Centre for Human Retrovirology

- Clinical colleagues

Prof Graham Taylor: HTLV/HIV

Dr Divya Dhasmana: HTLV/HIV

Dr Dan Bradshaw: UK HSA/ HTLV

Dr Nick Davies: Neuro infection

Adine Adonis: Neurophysio

Jo Keating: neurophysio

Jerico Beylon: HTLV ANP

Admin team

Darshna Makwana & Rita Kaur

Research Group Leaders @Imperial

Graham Taylor

Aileen Rowan

Goedele Marteens

Patients in the clinic & families

www.htlv.eu

HTLV channel YouTube (Portuguese)

<https://www.htlvaware.com/> (Spanish site link)

10th November: World HTLV day





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

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

Advances in Stem Cell Transplant for ATLL

Ali Bazarbachi
American University Of Beirut Medical Center (aubmc), Lebanon



AMERICAN
UNIVERSITY OF BEIRUT
FACULTY OF MEDICINE



AMERICAN
UNIVERSITY OF BEIRUT
MEDICAL CENTER
المركز الطبي في الجامعة الأميركية في بيروت

Advances in Stem Cell Transplant for ATL

Ali Bazarbachi, MD, PhD
American University of Beirut
Beirut, Lebanon



IACRLRD
International Association
for Comparative Research
on Leukemia and Related Diseases



ACADÉMIE
NATIONALE
DE MÉDECINE



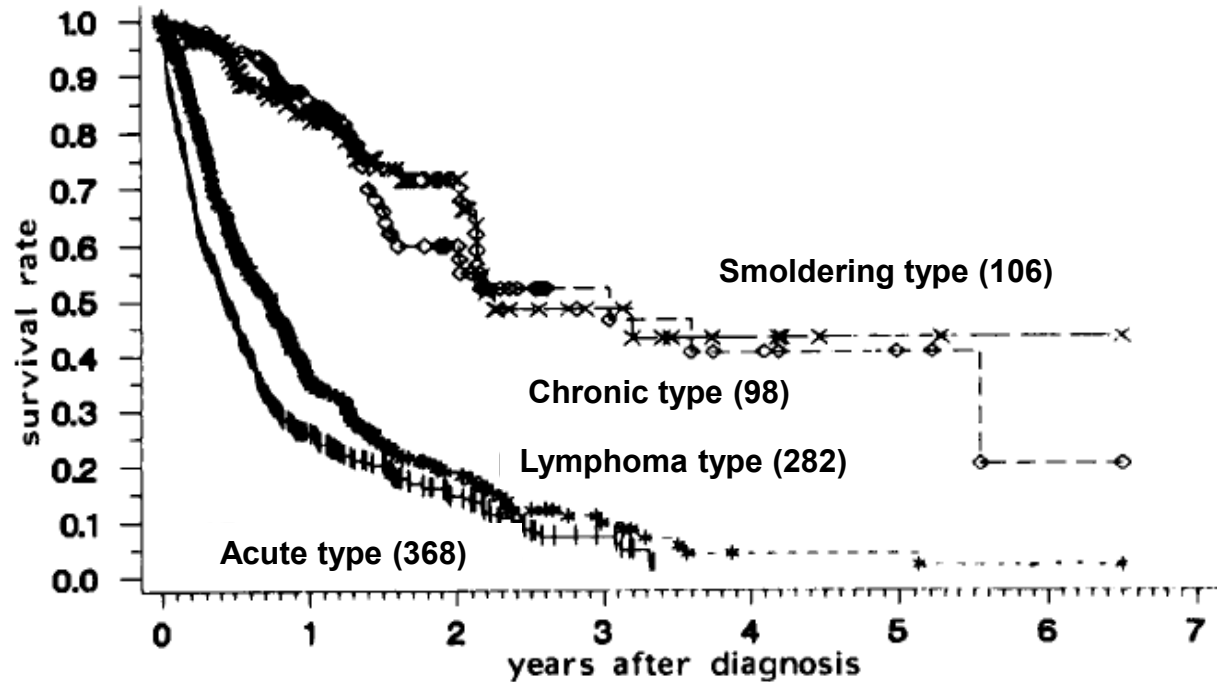
Conflicts of interest

Speaker bureau(s) or advisory board: Roche, Takeda, Biologix, Janssen, MSD, Pfizer and Amgen

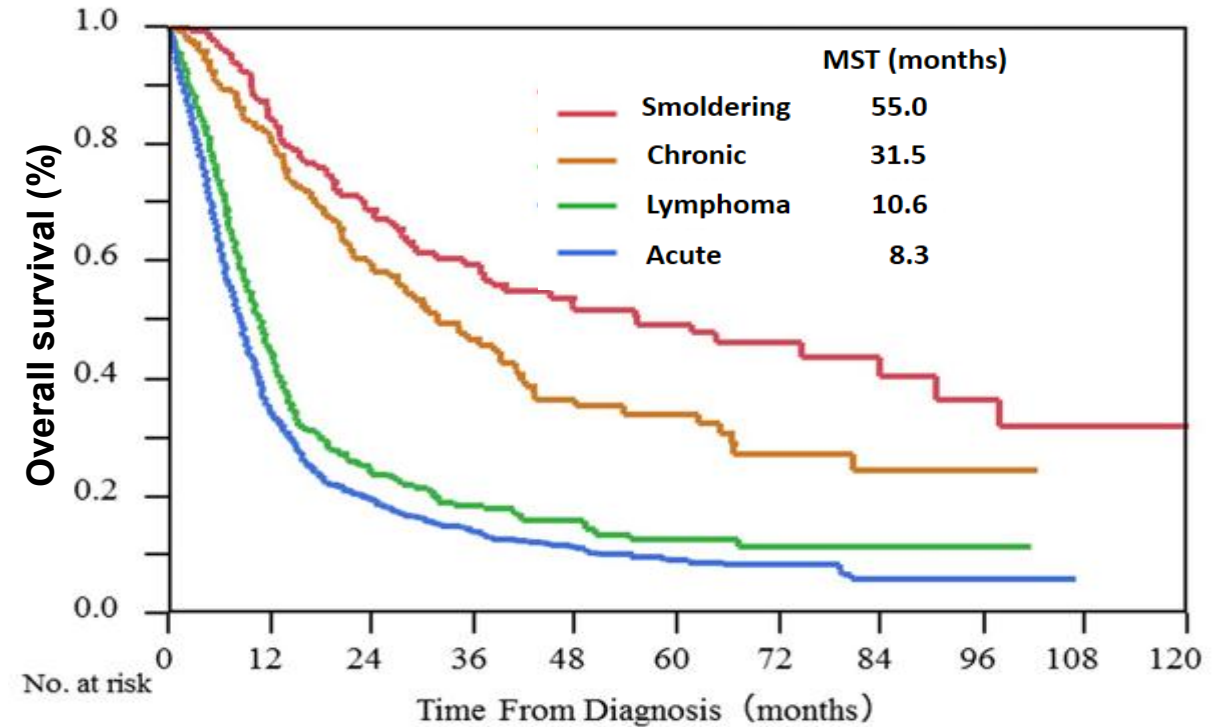
Research support: Novartis, Roche, Takeda, Biologix, Pfizer and Janssen

ATL has a dismal prognosis

Overall survival of ATL in Japan



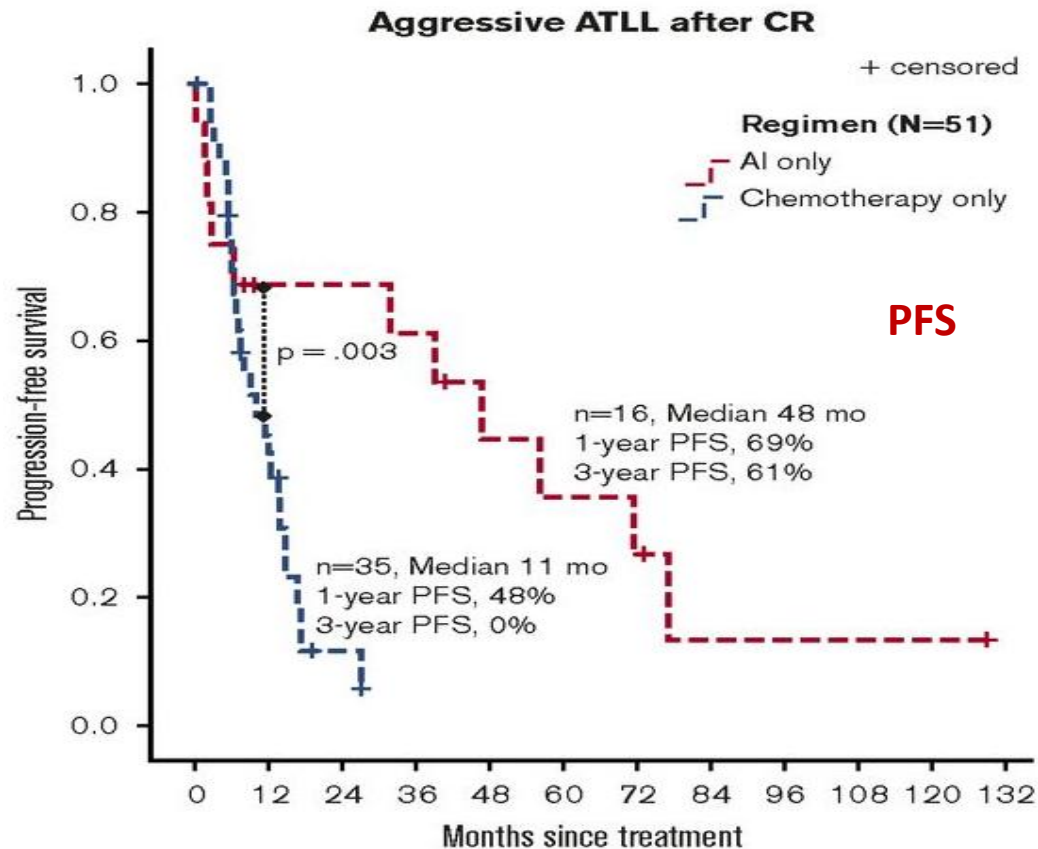
Shimoyama et al., 1992



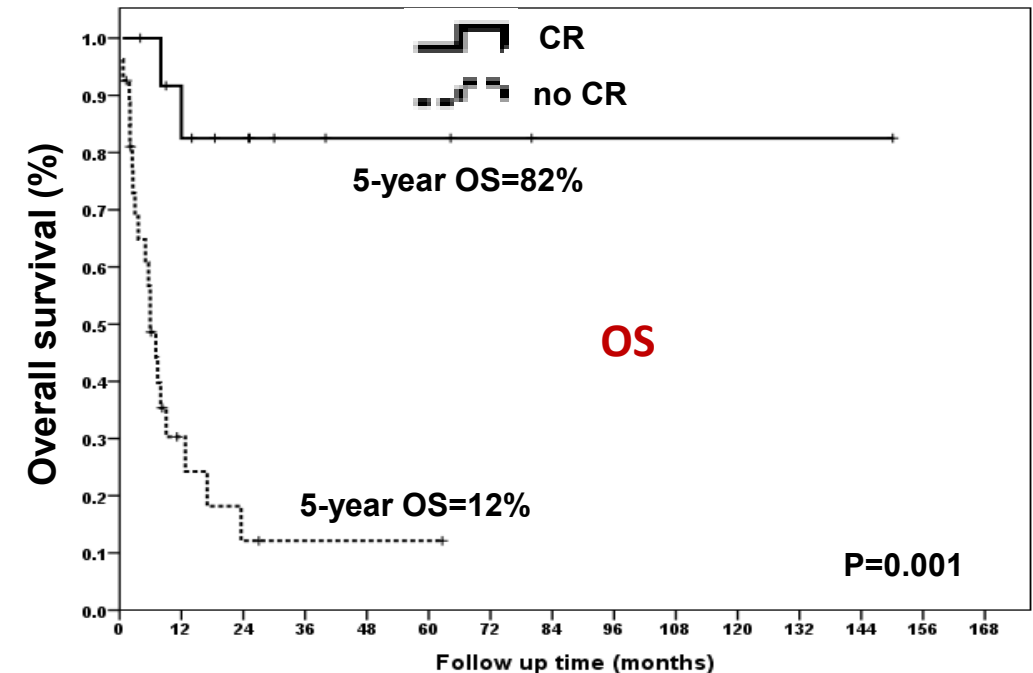
Katsuya H, et al. Blood 2015

After 3 decades, OS has not improved!

Outcomes of aggressive ATL in CR if no transplant



Malpica et al. Blood advances 2018

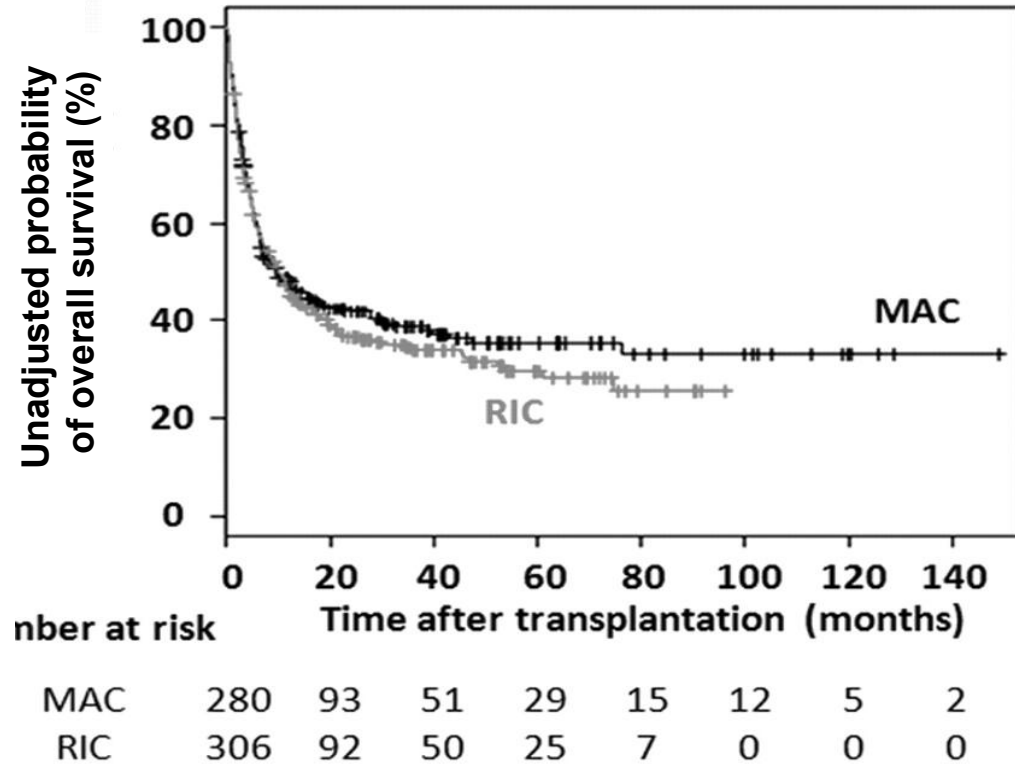


Bazarbachi A. et al. JCO 2010

- CR is short lived after chemo alone (Malpica et al. Blood advances 2018)
- Prolonged PFS and OS if CR after AZT/IFN particularly in acute ATL likely because of continuous therapy (frequent relapse after stopping treatment)

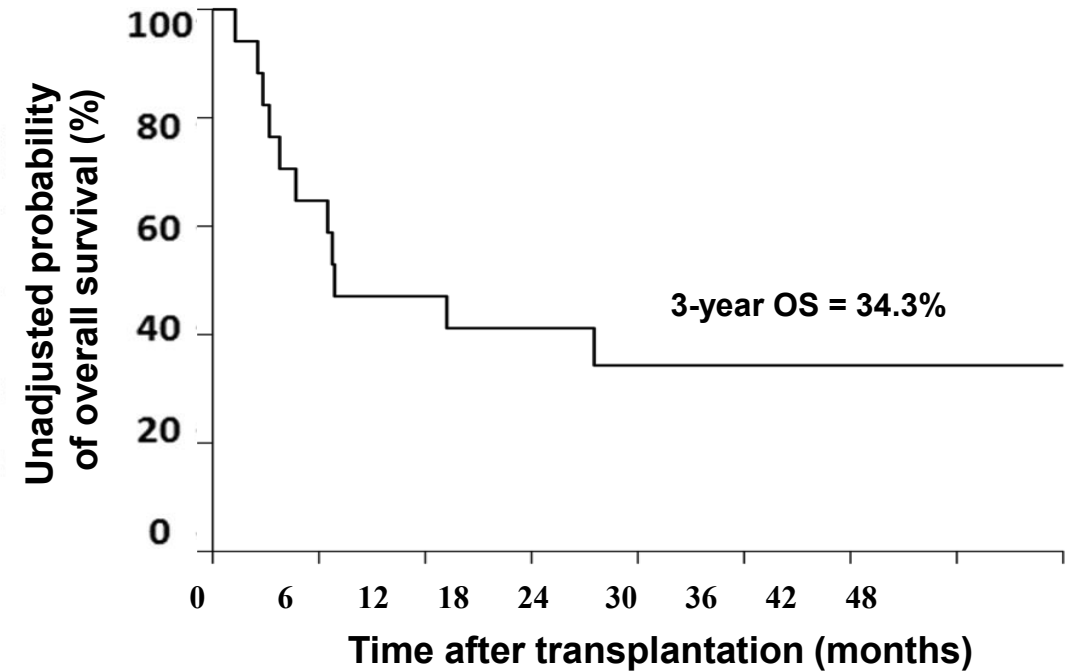
Allogeneic Stem Cell Transplantation: the past

Japanese Nationwide study



Ishida T et al. Blood 2012;120:1734-1741

EBMT retrospective study

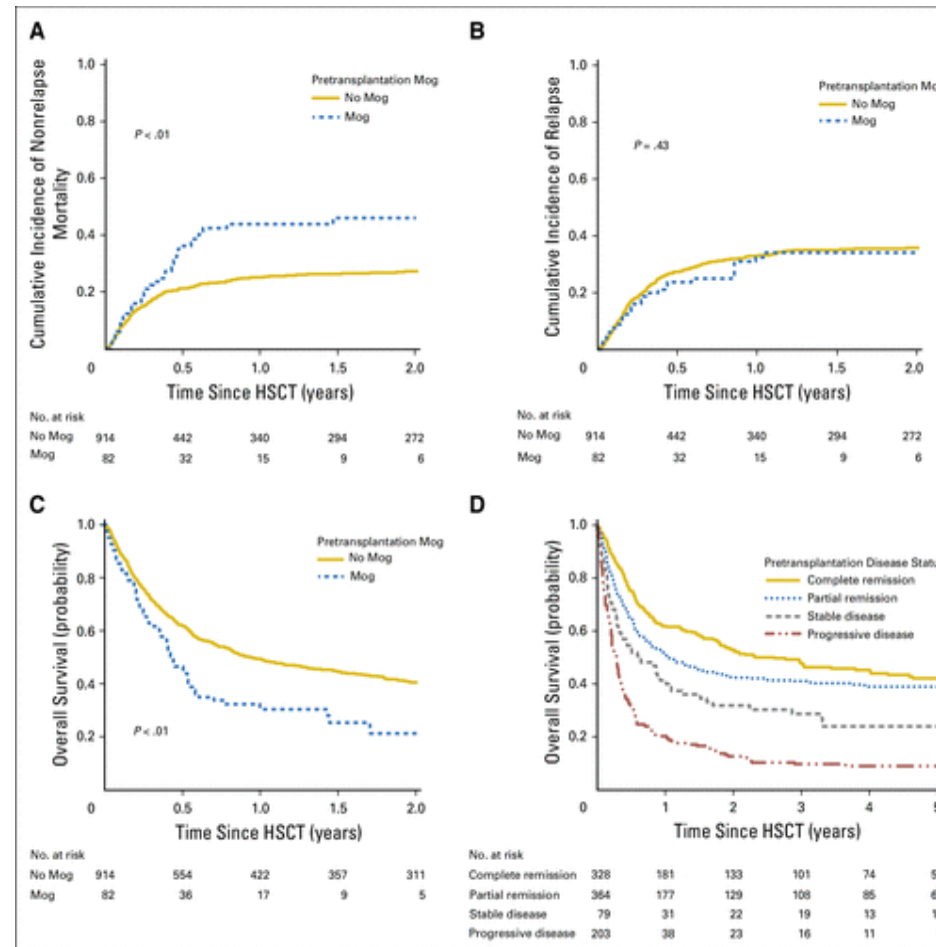


Bazarbachi et al. BMT, 2014

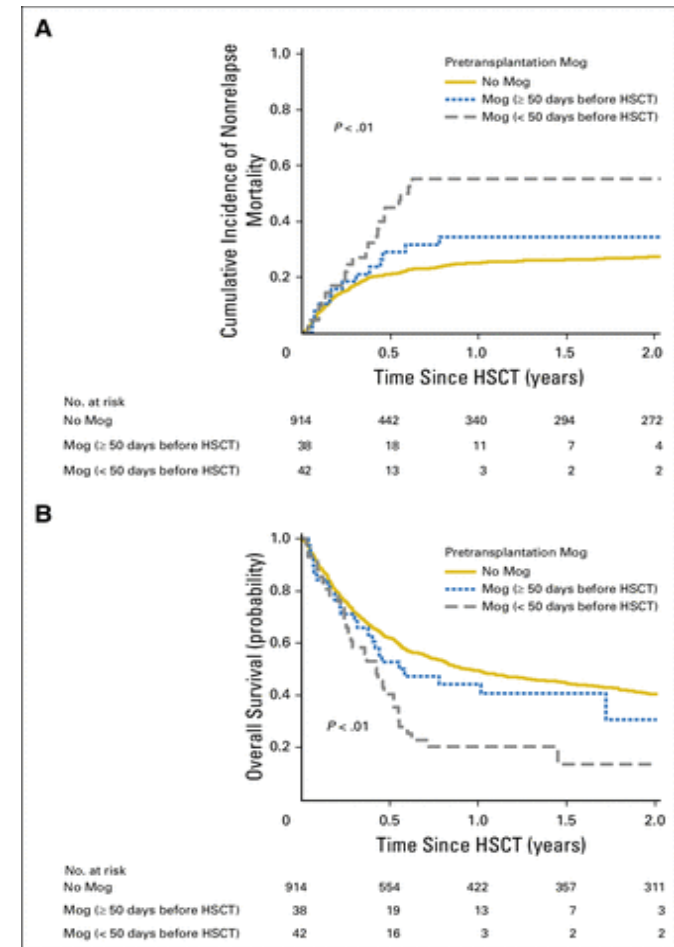
- ✓ Potentially curative: one third of transplanted patients
- ✓ Less than 10% of ATL patients reach transplant

Prior Mogamulizumab increases morbidity and mortality

- Treg lymphocytes express CCR4
- Grade 3/4 aGVHD (RR 1.80; $P < 0.01$)
- Steroid Refractory aGVHD (RR, 2.09; $P < 0.01$).
- One-year CI of NRM (44% v 25%; $P < 0.01$).
- One-year OS (32% v 49%; $P < 0.01$).

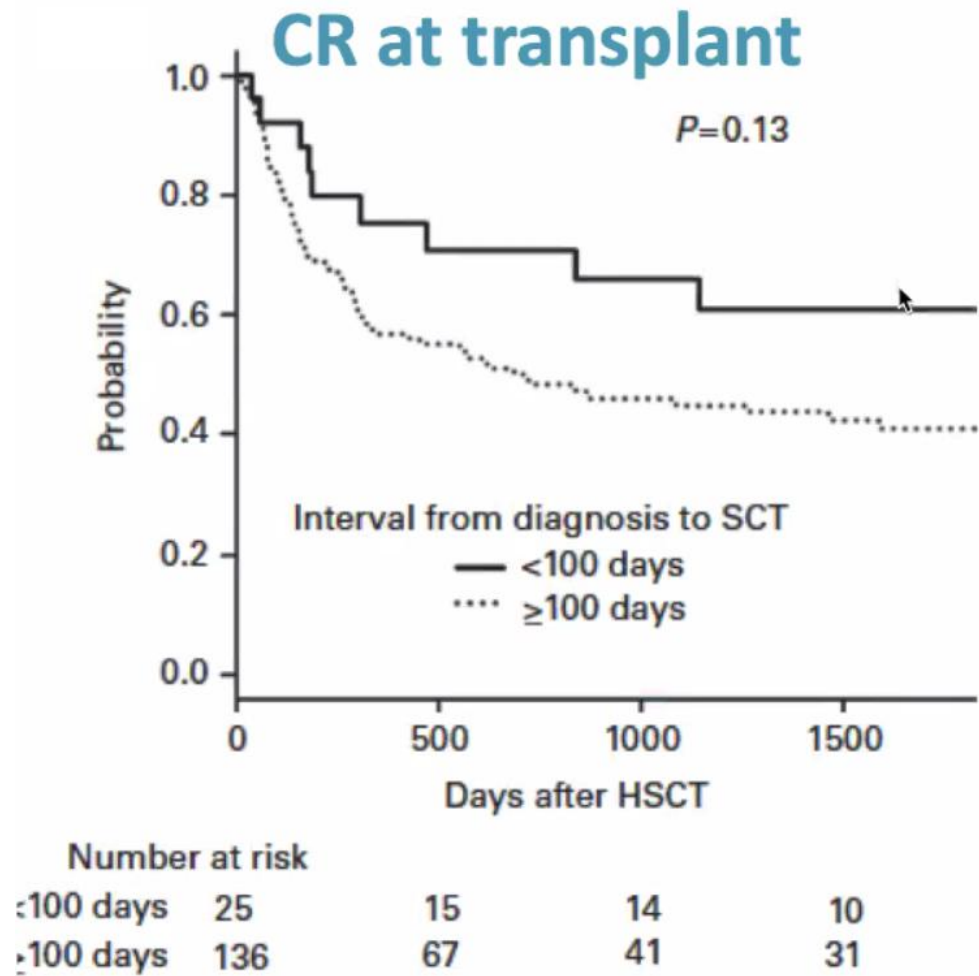


Allotransplant
effective in CR/PR

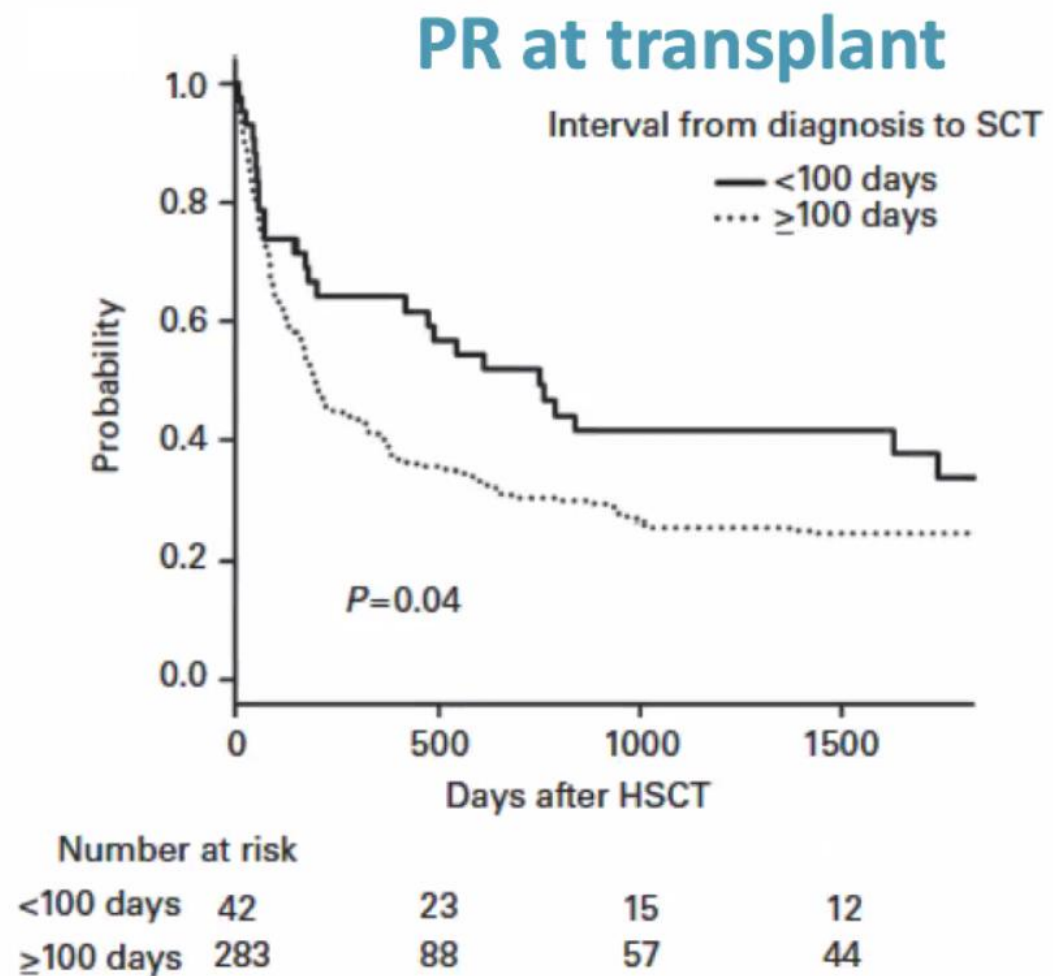


Moga <50 days
prior to allo-HSCT:
dismal outcomes

Impact of time from diagnosis to transplant and response at transplant on survival

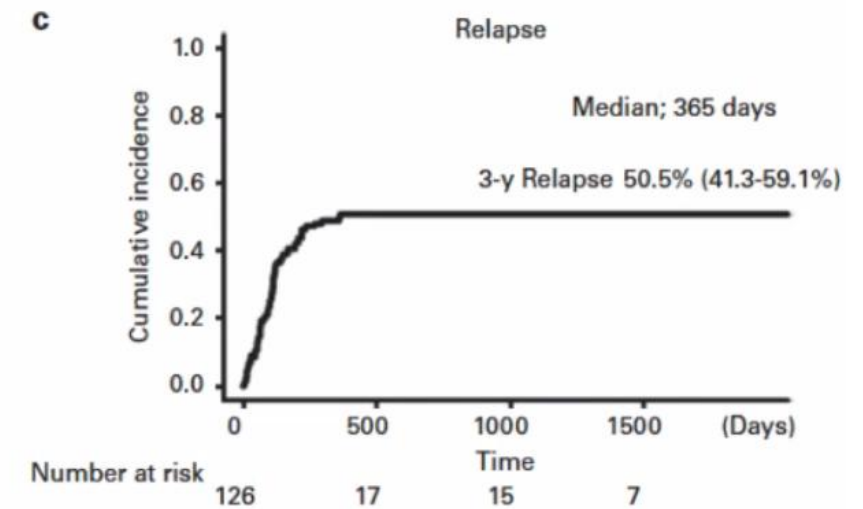
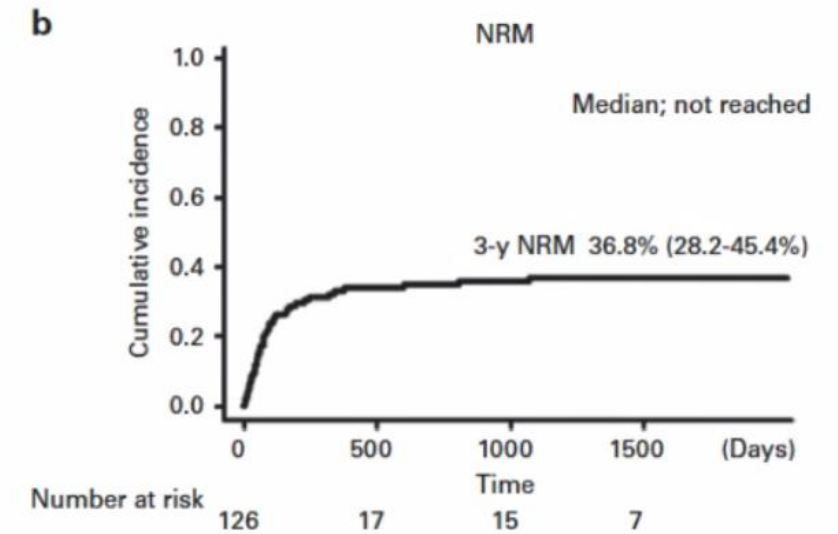
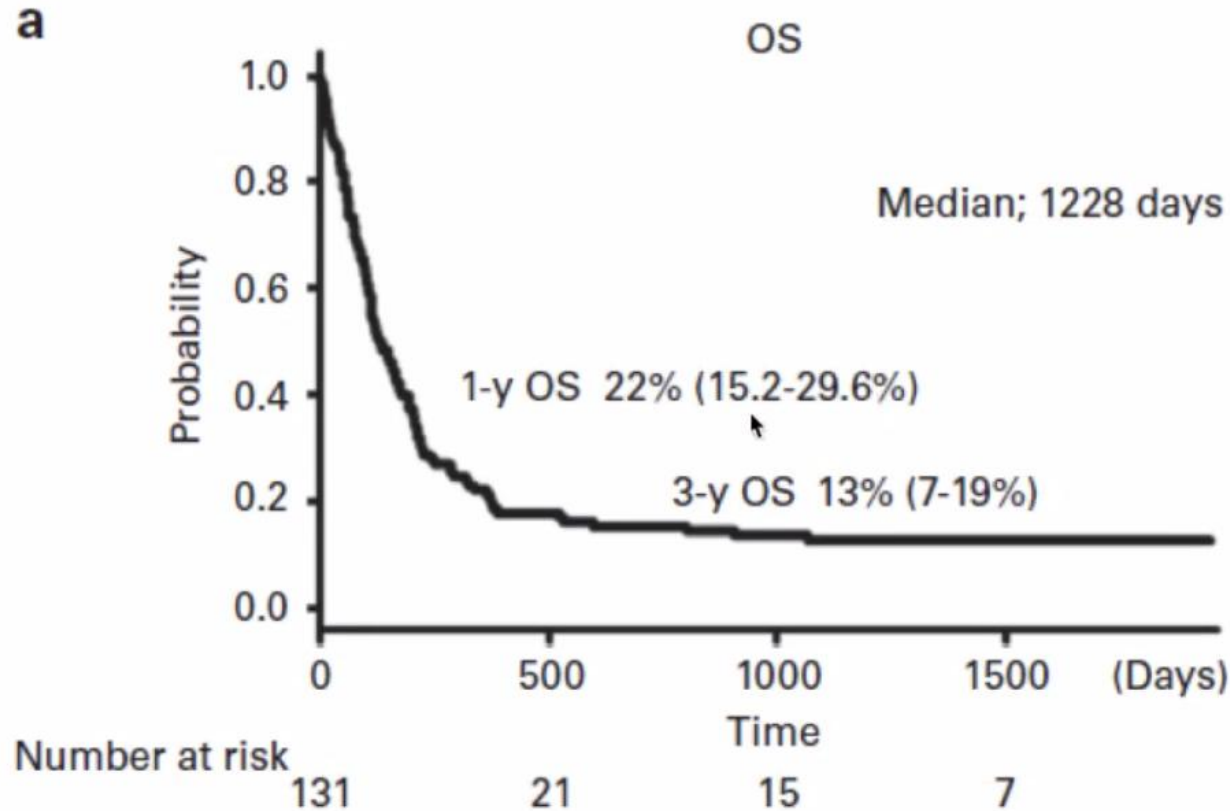


Patients in CR at time of transplant



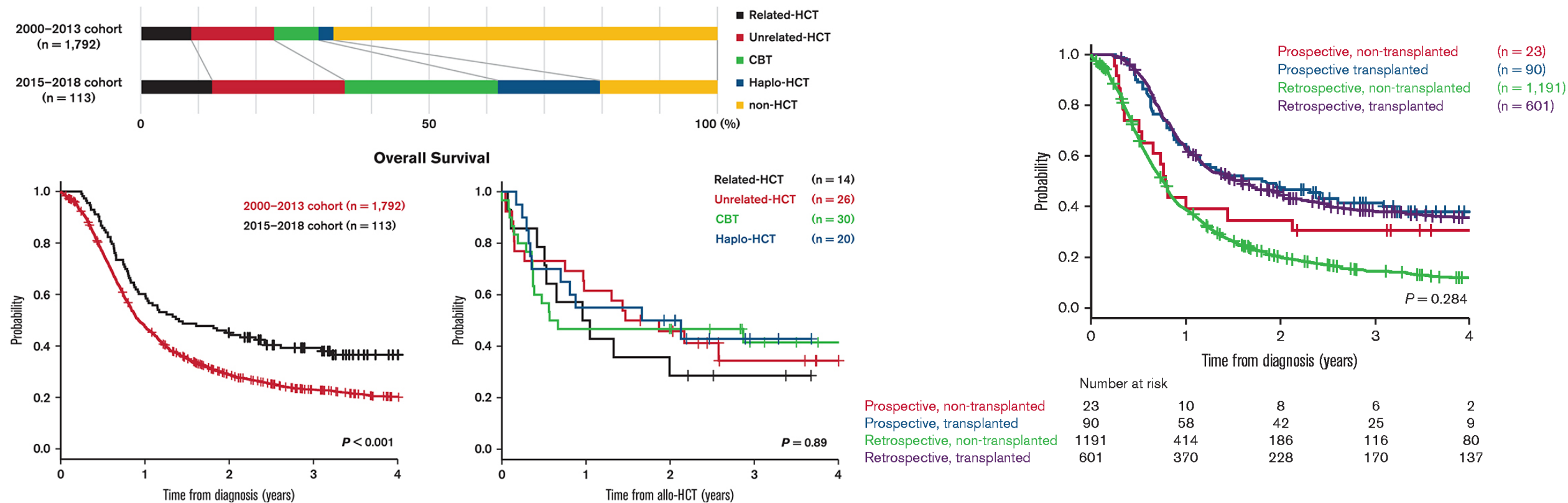
Patients in PR at time of transplant

Poor outcome of transplantation following relapse



Improved survival of patients with aggressive ATL by increased use of allo-HCT: a prospective observational study

Improved survival of patients with aggressive ATL by increased use of allogeneic HCT: A prospective observational study



Ito A. et al. Blood Adv. 2021

But survival of transplanted patients did not improve

North American Experience: improved survival with allo-HCT

ASCT Recipients:

- 1 acute; 4 lymphoma

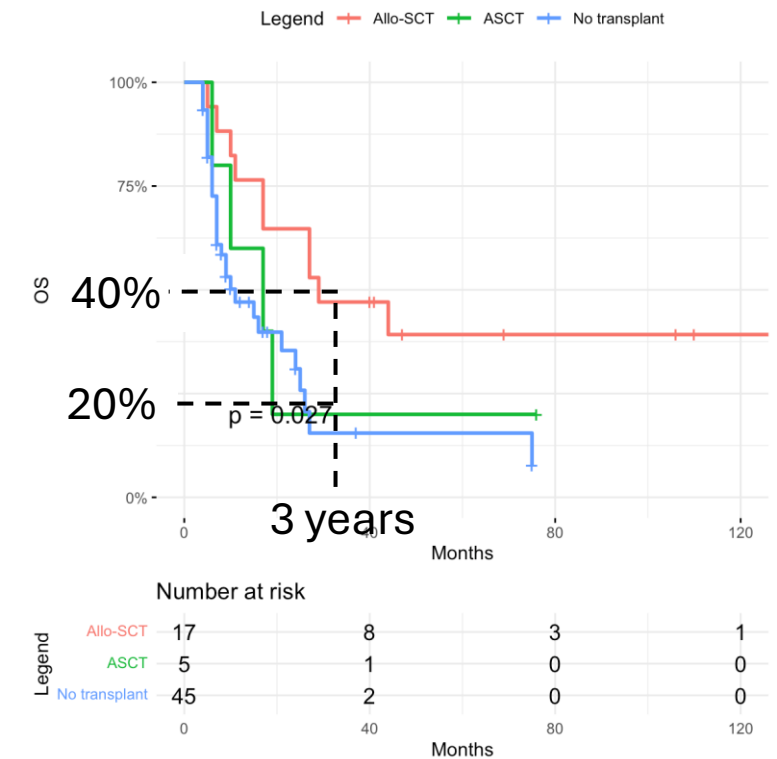
Allo Recipients:

- 17 ATLL (9 acute; 8 lymphoma).
- Median age was 56 years (18-74); KPS $\geq 90\%$ in 76.5%
- Median time from diagnosis to allo-SCT 9 months (range 4-378).
- At transplant: 47.1% CR, 17.6% PR, and 35.2% PD
- Allo-SCT from 2012-2020
- Donors: MRD 41.2%; MUD 17.6%; Haplo 35.3%; Syngeneic 5.9%.

No Transplant:

- 78 ATLL (57 acute; 10 lymphoma)
- ✓ **Transplant in first CR significantly improves outcomes**
 - ✓ **Patients with bad performance status (KPS < 90) have dismal outcomes**

Landmark analysis at 4 months



Upfront allo-HSCT after intensive chemotherapy for untreated aggressive ATL: JCOG0907, a single-arm, phase 3 trial

Takuya Fukushima, Kunihiro Tsukasaka, Ryunosuke Machida, Dai Maruyama, Shinichi Makita, Shigeru Kusumoto, Shinsuke Iida, Masahiro Tokunaga, Yasushi Miyazaki, Makoto Yoshimitsu, Ilseung Choi, Sawako Nakachi, Kana Miyazaki, Junya Makiyama, Kisato Nosaka, Hiroo Katsuya, Toshiro Kawakita, Taro Shibata, Haruhiko Fukuda, Hirokazu Nagai

Patient flow diagram

6

All enrolled patients* n=110
• eligible n=105
• ineligible n=5

Accrual period:
September 2010-June 2020

*excluding one patient with no informed consent document

Induction chemotherapy n=110

Acquisition of donor according to study defined procedures n=49

No acquisition of donor according to study defined procedures n=61

n=41

Study-transplantation n=41
(MAST n=19/RIST n=22)
(related n=12/unrelated n=29)

n=8

No study-transplantation n=69

Upfront
Transplantation
n=76

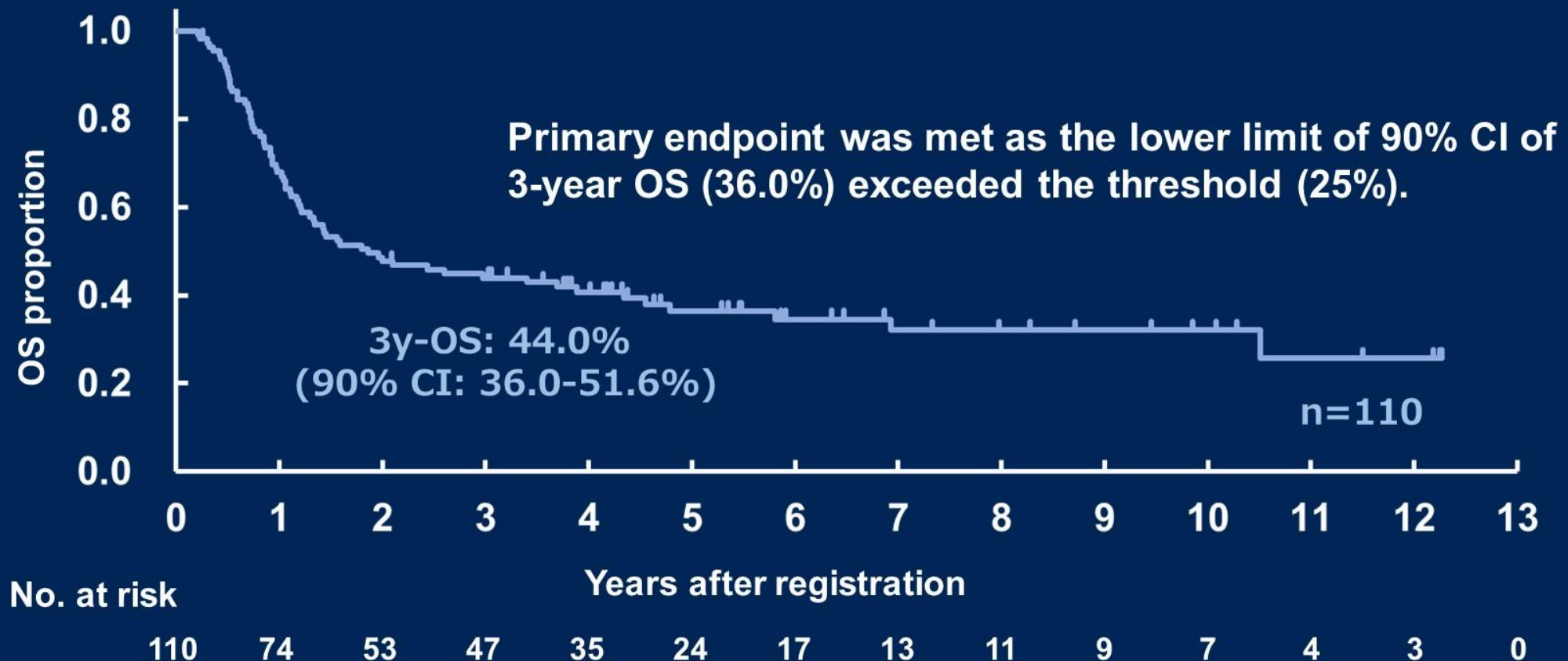
Transplantation as post-study treatment n=51
• MAST n=11 / RIST n=40
• related n=11 / unrelated n=15 / cord blood (CB) n=25

No transplantation
n=18

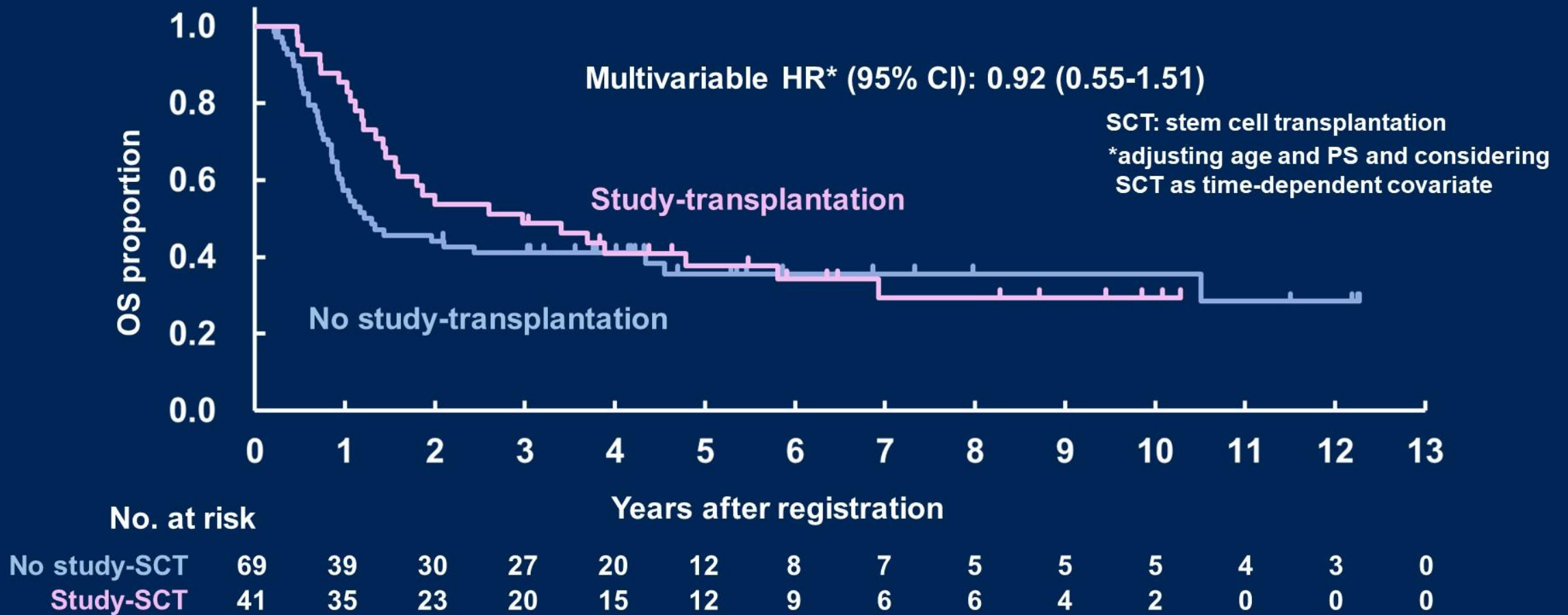
Transplantation in remission
n=35 (17 CB, 11 UR, 7 R)

Transplantation after progression/relapse
n=16 (8 CB, 4 UR, 4 R)

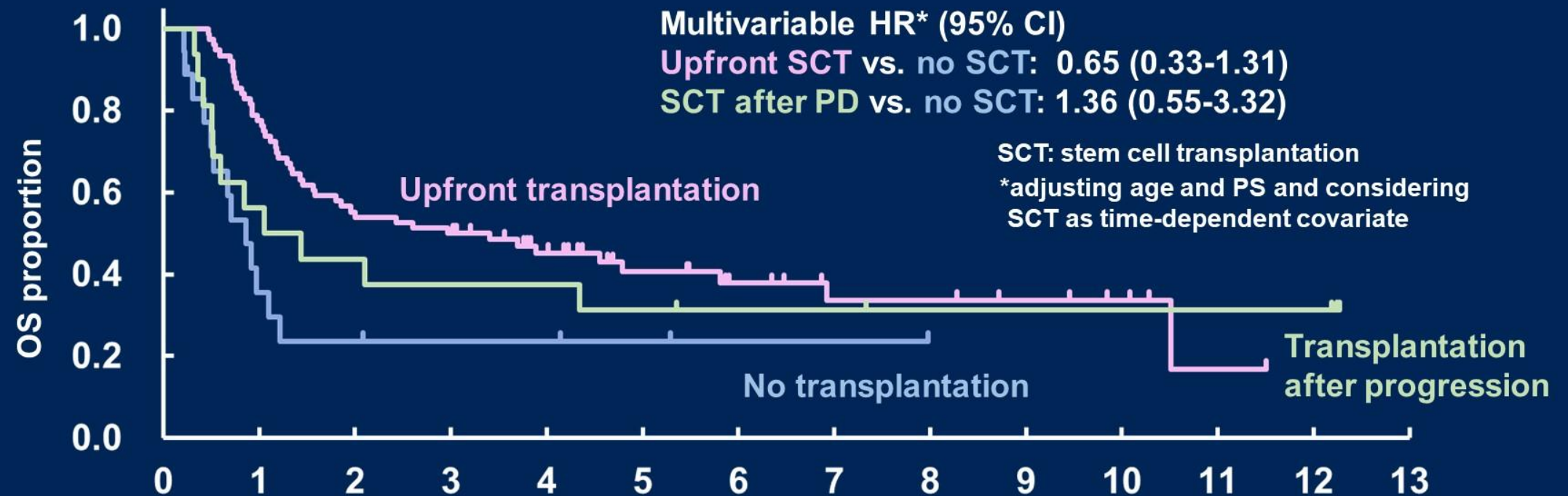
Overall survival for all evaluable patients



Overall survival for study-transplantation

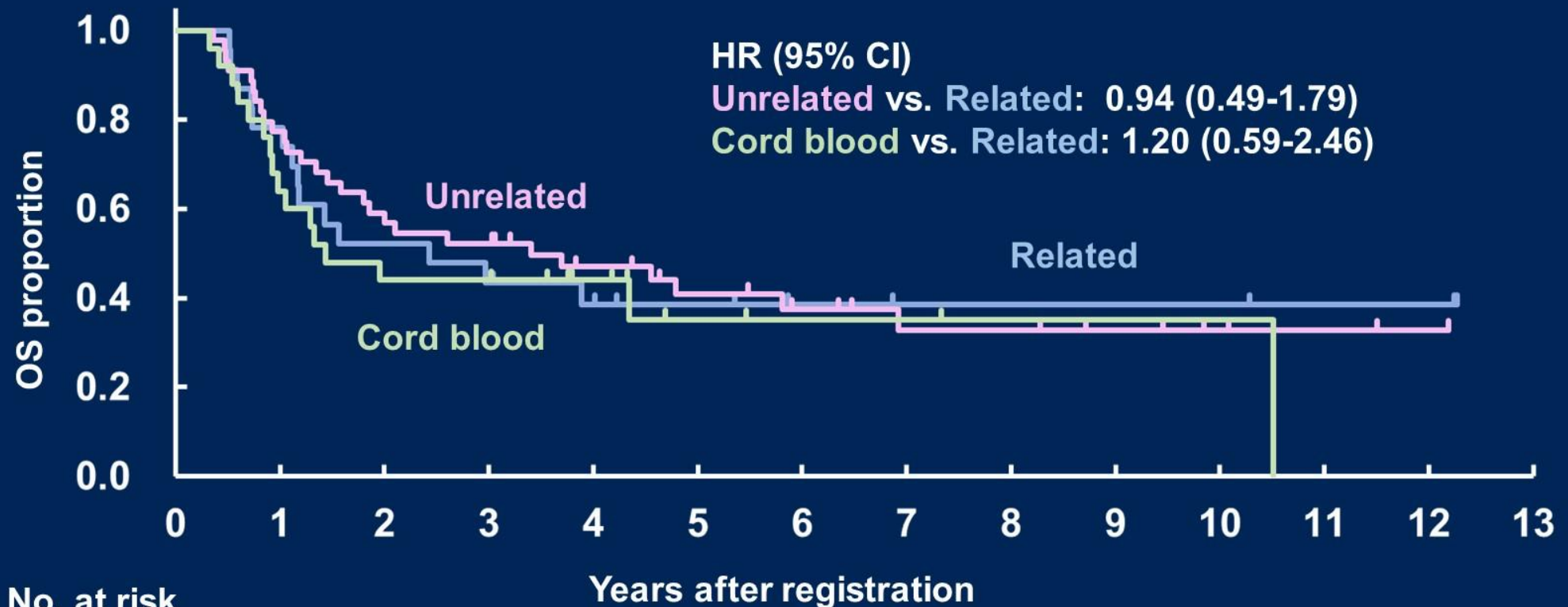


Overall survival for all upfront transplantation



No. at risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13
No SCT	18	6	4	3	3	2	1	1	0	0	0	0	0	0
Upfront SCT	76	59	42	38	26	17	12	8	8	6	4	1	0	0
SCT after PD	16	9	7	6	6	5	4	4	3	3	3	3	3	0

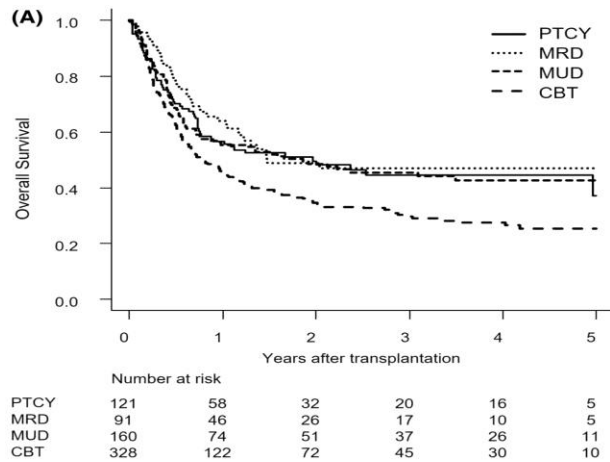
Overall survival according to donor source



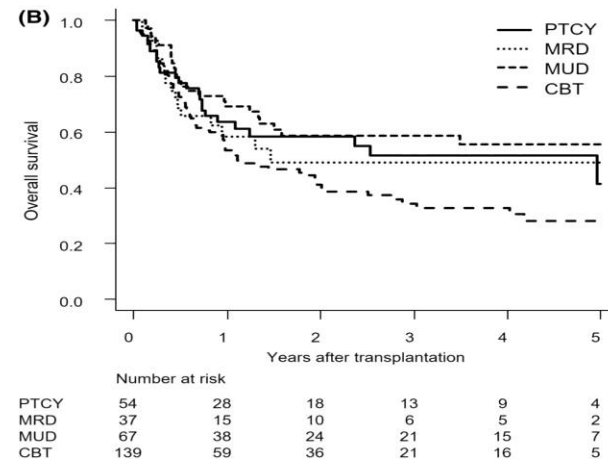
No. at risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Related	23	18	12	10	8	6	4	3	3	3	3	2	2	0
Unrelated	44	34	26	23	17	13	10	7	7	5	3	2	1	0
Cord blood	25	16	11	11	7	3	2	2	1	1	1	0	0	0

Outcomes according to donor type

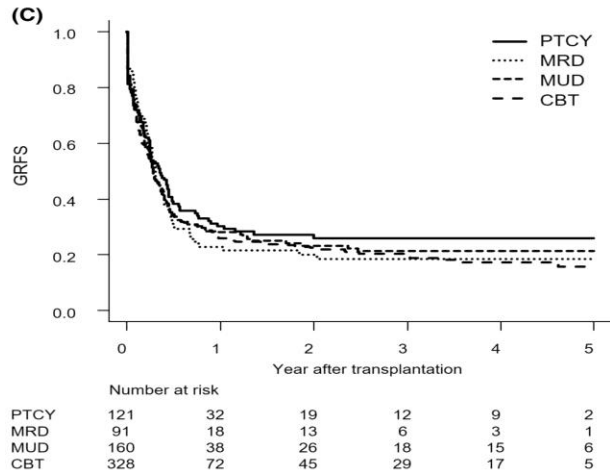
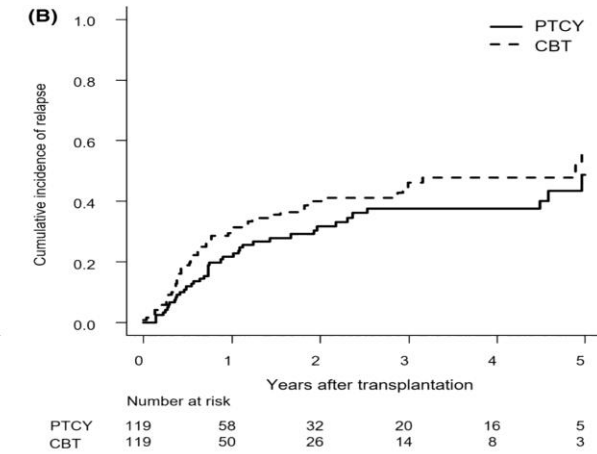
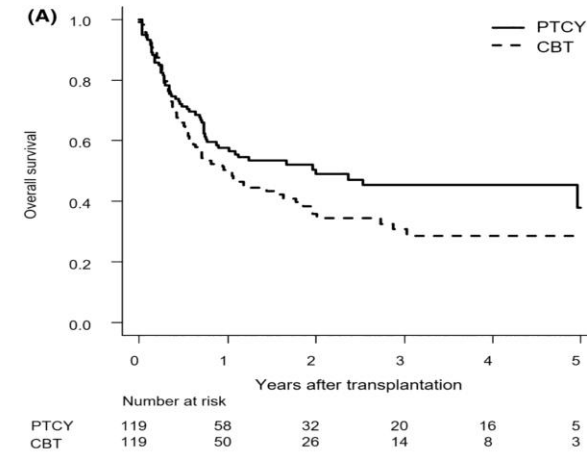
All patients



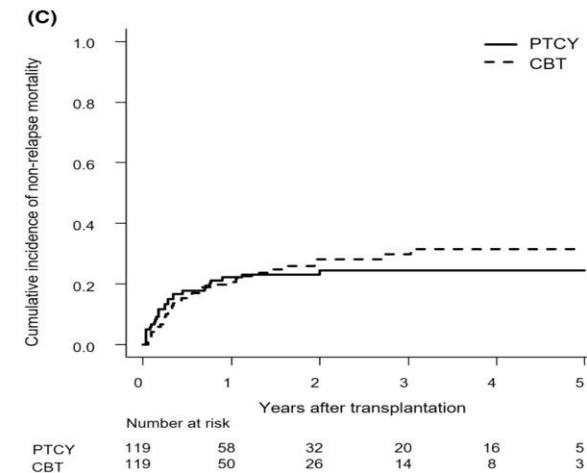
Patients in CR



Propensity score matching



**Inferior outcomes
with CBT**



**Stronger GVL
effect with Haplo**

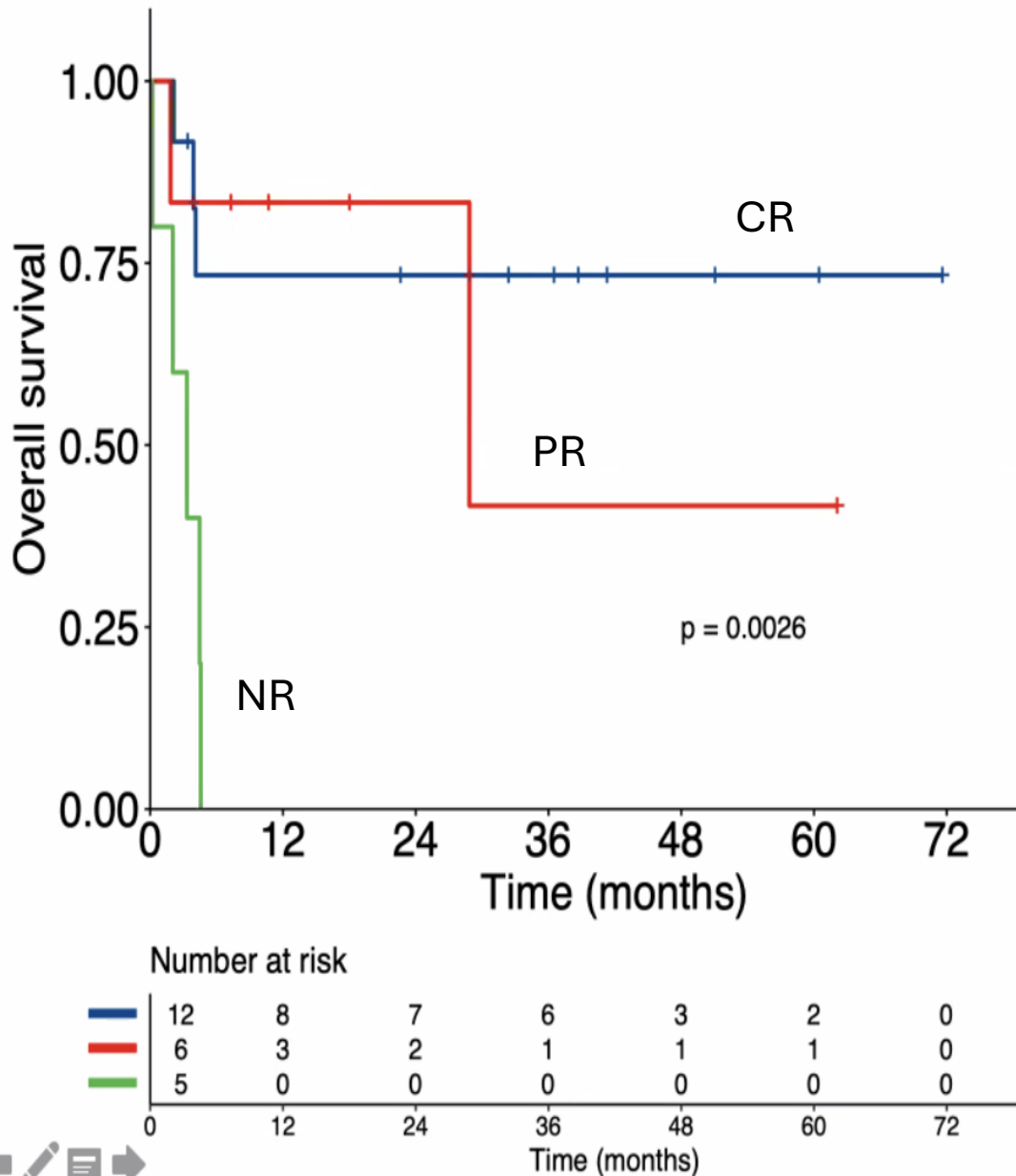
Table 2

Characteristic	Overall N = 39 ¹	MSD N = 10 ¹	haplo- identical N = 22 ¹	unrelated N = 7 ¹	p-value ²
Period					0.8
after 2019	29 (74%)	7 (70%)	16 (73%)	6 (86%)	
before 2019	10 (26%)	3 (30%)	6 (27%)	1 (14%)	
Age	50 (41, 59)	47 (36, 56)	55 (44, 62)	49 (35, 55)	0.4
Sex					0.081
F	24 (62%)	4 (40%)	17 (77%)	3 (43%)	
M	15 (38%)	6 (60%)	5 (23%)	4 (57%)	
ATL subtype					>0.9
acute/chronic aggressive	19 (49%)	5 (50%)	11 (50%)	3 (43%)	
lymphoma	20 (51%)	5 (50%)	11 (50%)	4 (57%)	
Skin involvement	15 (38%)	2 (20%)	8 (36%)	5 (71%)	0.12
Hypercalcemia	14 (36%)	3 (30%)	8 (36%)	3 (43%)	>0.9
JCOG prognostic index					0.4
high risk	18 (46%)	3 (30%)	12 (55%)	3 (43%)	
moderate risk	21 (54%)	7 (70%)	10 (45%)	4 (57%)	
CNS involvement	6 (15%)	1 (10%)	5 (23%)	0 (0%)	0.5
Number of lines					0.5
1 line	28 (72%)	6 (60%)	16 (73%)	6 (86%)	
more than 1 line	11 (28%)	4 (40%)	6 (27%)	1 (14%)	
Disease status at allo-HSCT					0.8
CR	27 (69%)	7 (70%)	16 (73%)	4 (57%)	
NR	7 (18%)	2 (20%)	4 (18%)	1 (14%)	
PR	5 (13%)	1 (10%)	2 (9.1%)	2 (29%)	
Donor HTLV1 serology					0.2
NEG	36 (92%)	8 (80%)	21 (95%)	7 (100%)	
POS	3 (7.7%)	2 (20%)	1 (4.5%)	0 (0%)	

Necker Experience

Characteristic	Overall N = 39 ¹	MSD N = 10 ¹	haplo- identical N = 22 ¹	unrelated N = 7 ¹	p-value ²
Graft source					<0.001
BM	16 (41%)	0 (0%)	16 (73%)	0 (0%)	
PBMC	23 (59%)	10 (100%)	6 (27%)	7 (100%)	
Conditioning					>0.9
T1B2F	32 (82%)	8 (80%)	18 (82%)	6 (86%)	
T2B2F	7 (18%)	2 (20%)	4 (18%)	1 (14%)	
PTCy	24 (62%)	0 (0%)	22 (100%)	2 (29%)	<0.001
Time from chemo to allo-HSCT	159 (134, 203)	166 (154, 237)	159 (134, 190)	138 (124, 203)	0.7

Overall survival

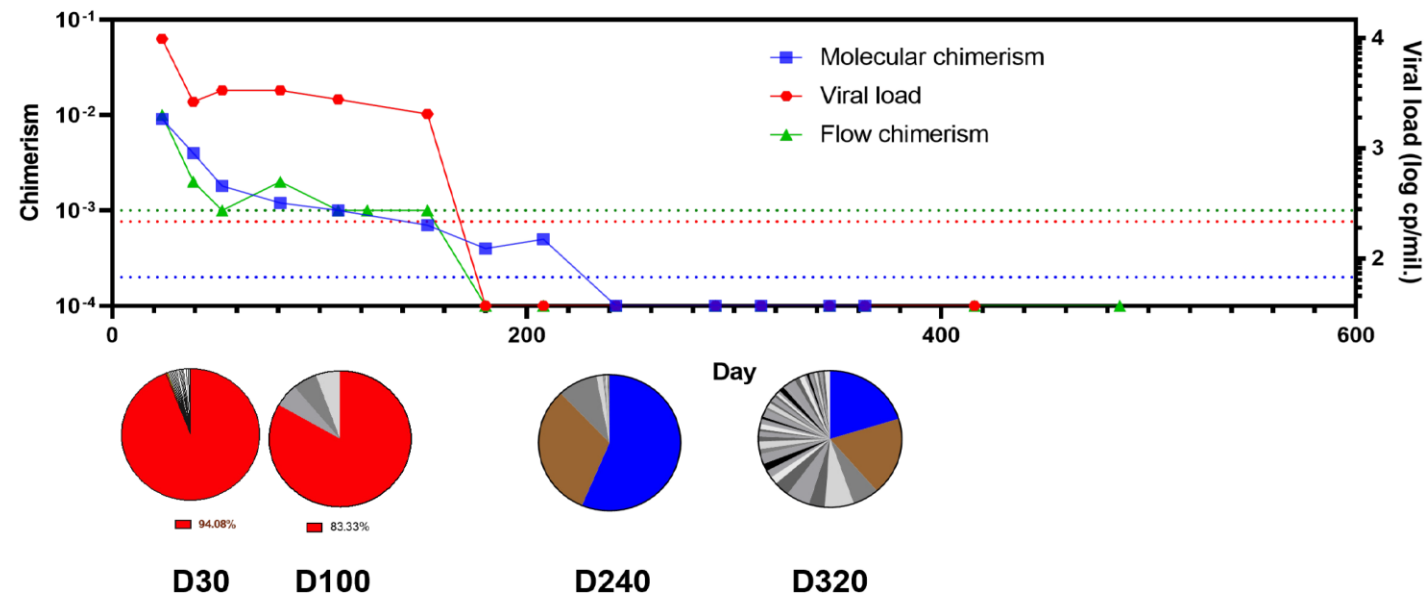
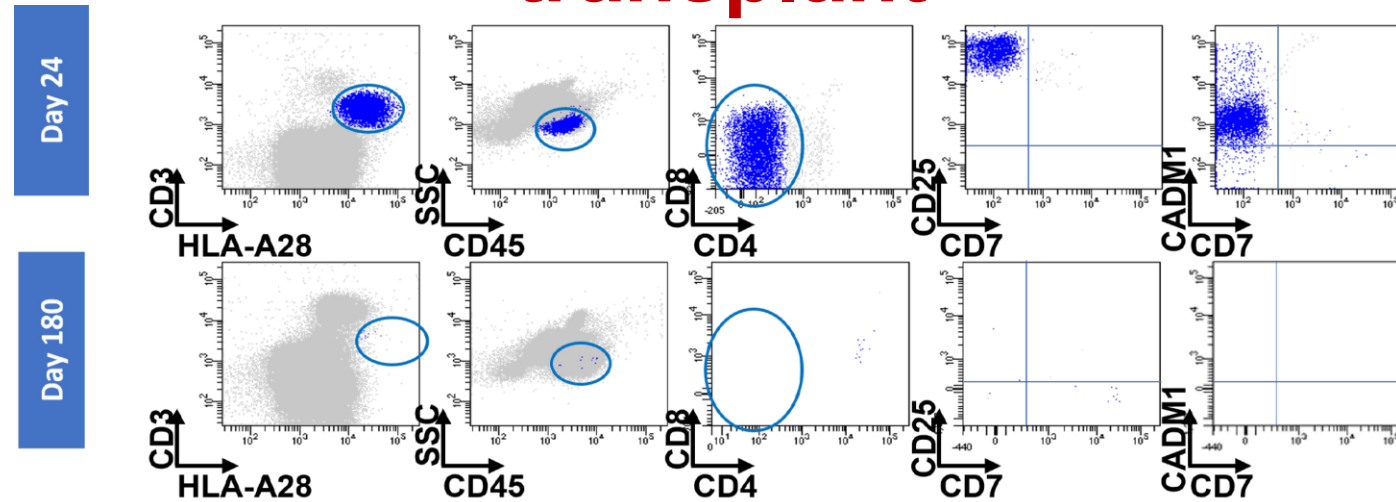


Survival according to disease status at time of alloSCT	OS at two years	Median
CR	73% [51-1]	Not reached
PR	83% [58-1]	Not reached
SD/PD	0%	3 months

Cause of death

- Intestinal acute GVHD (n=2)
- MOF (n=1) and hepatic failure (n=)
- Progression/relapse (n=6)

Evidence of MRD and HTLV-1 viral load eradication post transplant



Dedicated HTLV-1 follow up

Proviral load quantification (n=13 patients)

→ Negative proviral load in 12/13 (mean 60 days)

→ Two patients reverted to positive PvL at 12 and 30 months (PvL <1%), respectively while sustaining full donor chimerism.

→ One patient PvL : 0.2%, chimerism recipient : 0.11%

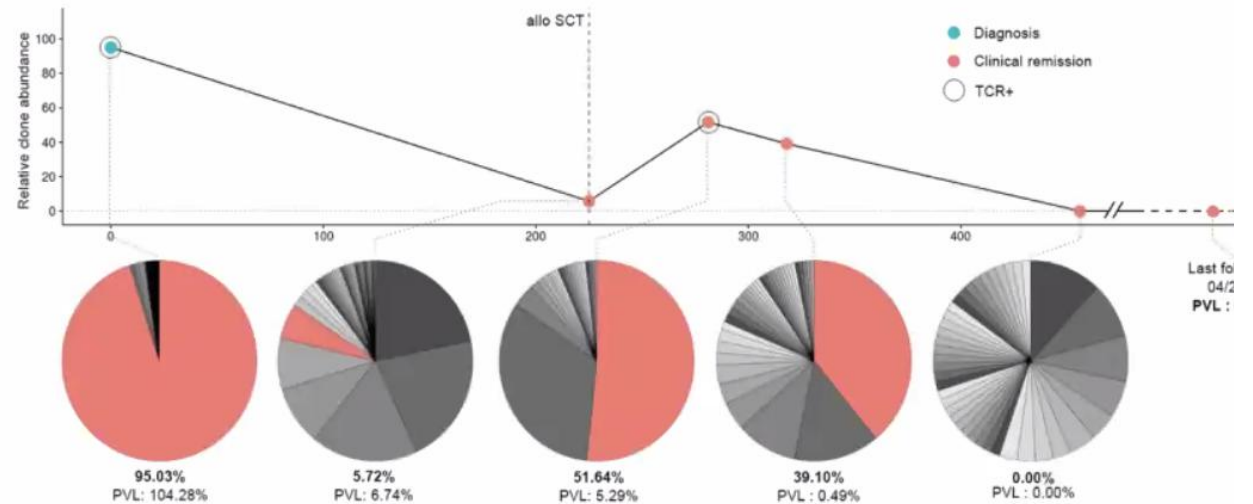
Clearance of the tumor viral clone assessed with HTS in leukemic subtypes

42 year old female

chemotherapy with BV-CHP et MTX HD→

partial remission

Allogeneic HSCT with MSD (HTLV-1 negative)



EBMT registry (2004-2021)



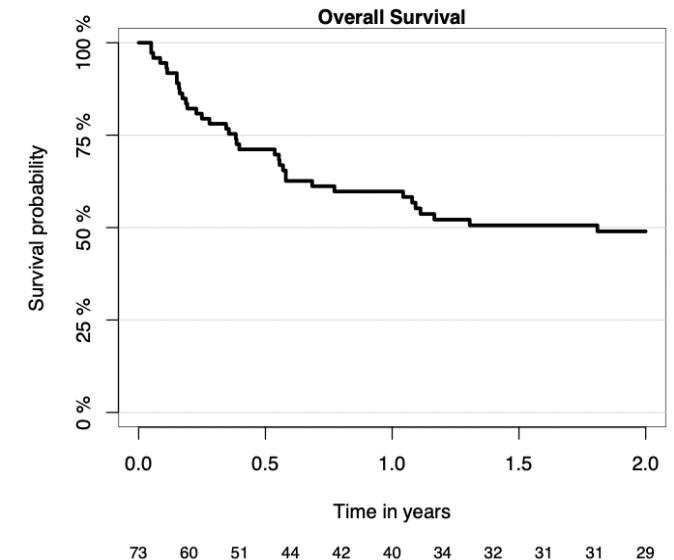
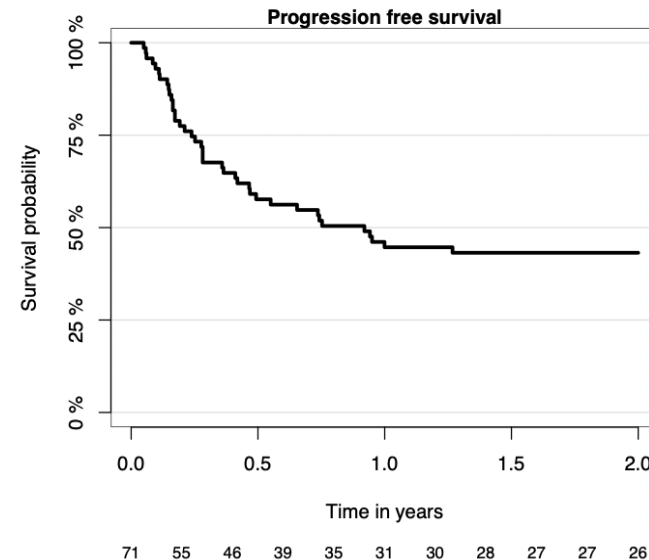
- 73 ATLL (19% acute; 73% lymphoma; 6% chronic and 2% smoldering).
- Median age: 45 years (26-67); KPS $\geq$ 90% in 74%
- Prior to transplant: 1 line: 64%, $\geq$ 2: 36%
- Median time first-line to allo: 7 months (range 1-93).
- At transplant: 69% CR, 21% PR, and 10% SD/PD.
- MRD 33%; UD 27%; Haplo 32%. 91% HTLV-1 negative
- PB 89%; BM 11%.
- Conditioning: RIC 79%; TBI 30%.
- GVHD prophylaxis: Calcineurin inh+MMF 59%; PTCy 38%; ATG 12%

Post transplant outcomes: EBMT registry



- Median FU of 3.9 years; 2-year OS 49%; PFS 43%
- **CR at transplant: OS 56% PFS 50% RI 44%**
- Non CR: at transplant OS 33% PFS 27% RI 63%
- No difference according to ATL subtype.
- **In MVA, CR at transplant, younger age, and haplo donors: independent predictors of OS**

Outcome	Estimation (95% CI)
Relapse incidence	49.8% (37.5-60.9)
Non-relapse mortality	7% (2.6-14.6)
aGVHD II-IV (100 days)	7.1% (2.6-14.8)
aGVHD III-IV (100 days)	4.3% (1.1-11)
cGVHD	37.6% (26.1-49)
Extensive cGVHD	17.7% (9.7-27.8)



NRM for HCT within 6.5 m from diagnosis
14% vs 0% (p=0.04)

International consensus statement

1. Up-front allo-HSCT should be considered for all suitable patients with aggressive ATL.
2. Early referral to a transplantation center is recommended.
3. HTLV-1 seronegative donors are preferred to reduce the risk of donor-derived ATL.
4. Mogamulizumab should not be used within 50 days of allo-HSCT.

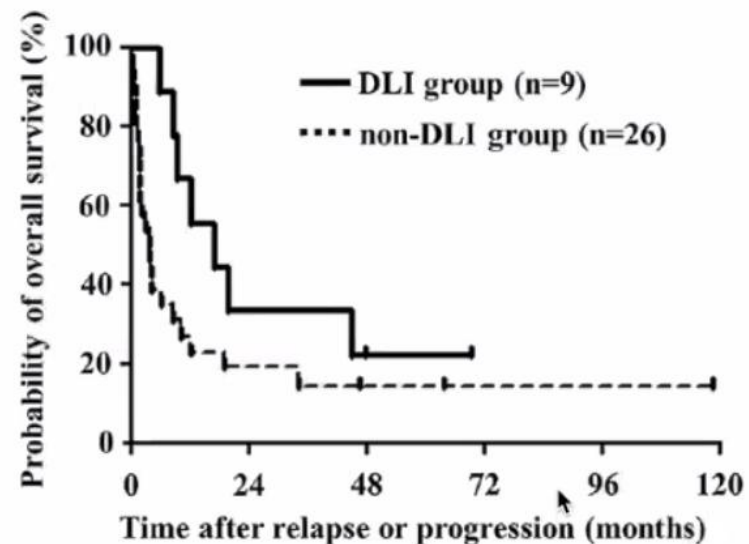
Allogeneic haematopoietic cell transplantation in PTCL: recommendations from the EBMT Practice Harmonisation and Guidelines Committee



Adult T-cell leukaemia lymphoma

- Assess eligibility for allo-HCT and consider donor search at diagnosis
- Allo-HCT should be considered as a **first-line treatment option as soon as CR, PR, or SD is reached**
- If allo-HCT not done in first-line, its use in R/R situations should be considered
- Pre-HCT moga should be avoided because of an increased risk of GVHD.
- BV-based therapies are recommended for CD30-positive cases
- Autologous HCT should not be proposed.
- RIC preferable and HTLV-1 negative donors are preferred.
- Donor selection: follows general recommendations, including haplo
- There is no standard post-transplantation maintenance.

Relapse after allo-HCT: benefit from DLI



Time of relapse after allo-SCT, mo	Tumor lesion at relapse	Pre-DLI therapy	Status at DLI	Time of DLI after relapse, mo	T-cell dose, $\times 10^6/\text{kg}$		Response to DLI	GVHD after DLI (type of cGVHD)	OS after relapse, mo	Cause of death
					Initial	Total				
1.0	Skin	Oral VP-16	NE	8.0	5.5	5.5	CR	Progression (extensive)	45.0	Infection
2.4	Skin, hypodermis	Half-dose CHOP	PD	0.6	10.0	110.0	PR	Emergence (extensive)	16.9	PD
2.8	CNS	IT	PR	0.4	10.0	40.0	CR	Absent	19.9	PD
100.7	Skin	RT	SD	1.0	12.0	221.0	CR	Emergence (limited)	47.7+	-
0.4	PB, liver, pleural effusion	Half-dose CHOP	PR	0.9	10.0	10.0	CR	Emergence (extensive)	69.4+	-
3.1	PB	No	PD	2.3	6.9	33.0	PD	Absent	8.7	PD
10.6	Bone, liver	No	PD	1.2	5.0	15.0	SD	No progression	9.2	PD
11.0	Lymph nodes	No	PD	1.4	5.0	65.0	SD	Progression (extensive)	5.7	PD
1.1	Hypodermis	RT	PD	5.0	8.2	40.8	PD	Progression (extensive)	12.1	PD

Management of post-transplant relapse



- Clinical trial
- Donor lymphocyte infusion
- Lenalidomide
- Valemestostat
- Mogamulizumab
- Zidovudine and interferon alfa
- Single agent chemotherapy such as etoposide
- Anti-PD-1 or anti-PD-L1 antibody treatment should be avoided, at least in monotherapy, to prevent the high risk of flare-up.



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

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

Current & emerging therapeutic strategies for ATLL in USA

Juan Carlos Ramos
University of Miami-Sylvester Comprehensive Cancer Center, USA

Current & emerging therapeutic strategies for ATLL in the U.S.A.

Juan Carlos Ramos, MD

Department of Medicine-Division of Hematology

Sylvester Comprehensive Cancer Center

University of Miami Miller School of Medicine

Adult T-cell leukemia-lymphoma (ATLL)

- A peripheral T-cell lymphoma (PTCL) caused by HTLV-1
- **CD4⁺ CD25⁺ CCR4⁺ CADM1⁺**
- Variable expression of **CD30** and **MUM-1(IRF-4)**
- Develops in 2-7% of HTLV-1 infected (6th-7th decades)
- 10-20 million are HTLV-1+ worldwide (more common in Japan, Africa, the Caribbean, and South America)
- Higher proportion of PTCL cases in Latin America (LATAM)

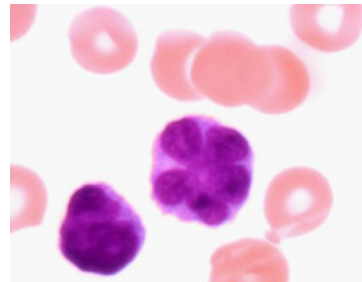
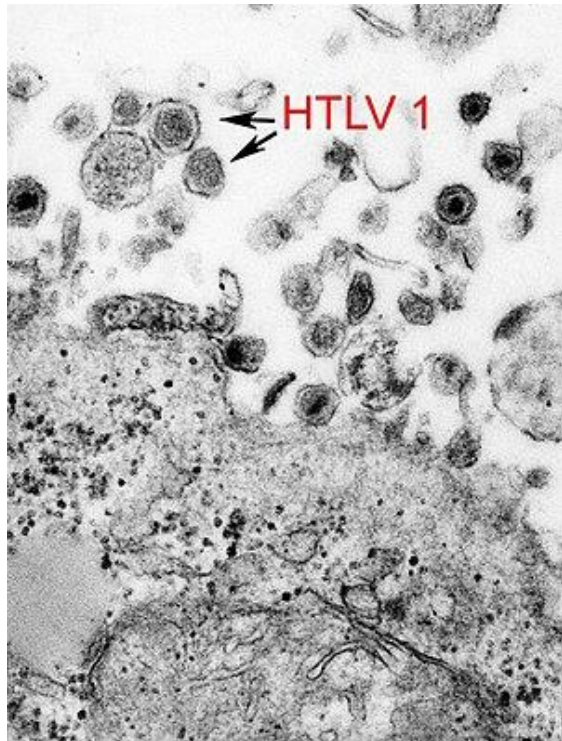
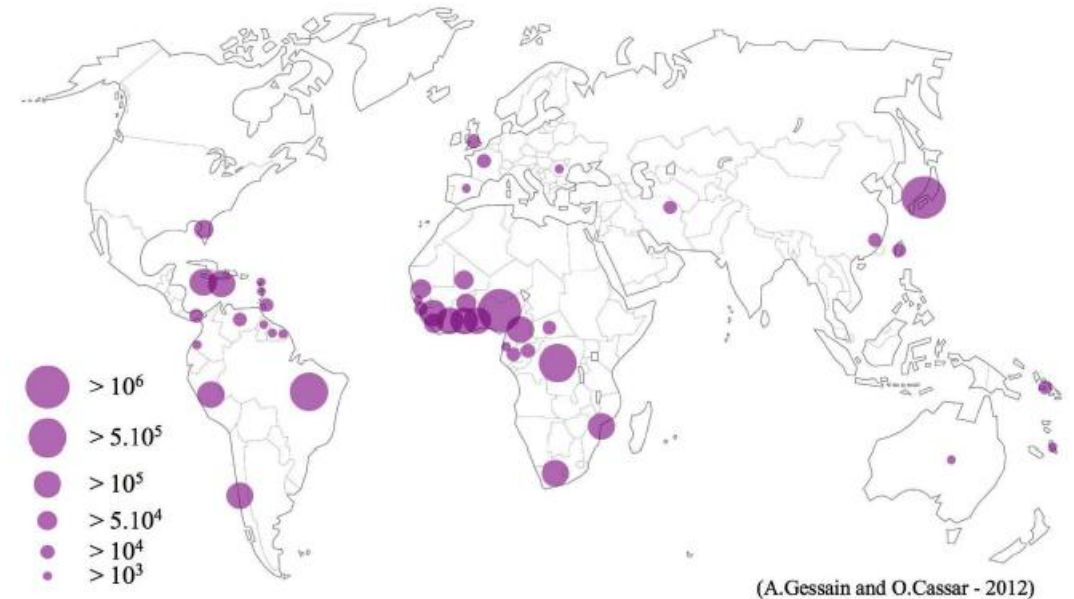


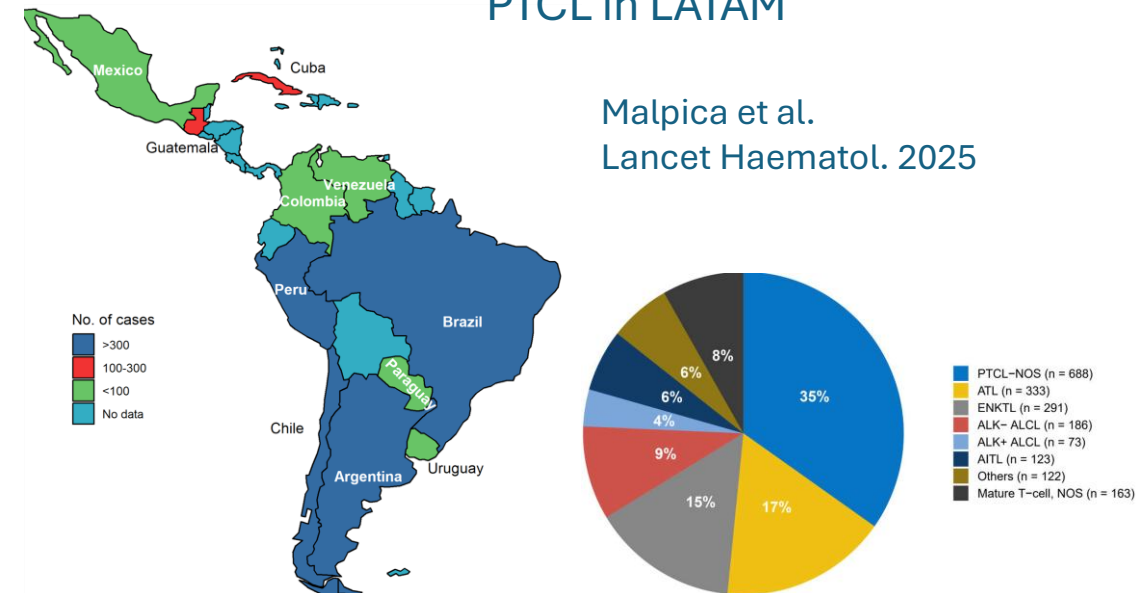
Image from Acute ATLL patient: University of Miami

HTLV-1 endemic regions



PTCL in LATAM

Malpica et al.
Lancet Haematol. 2025

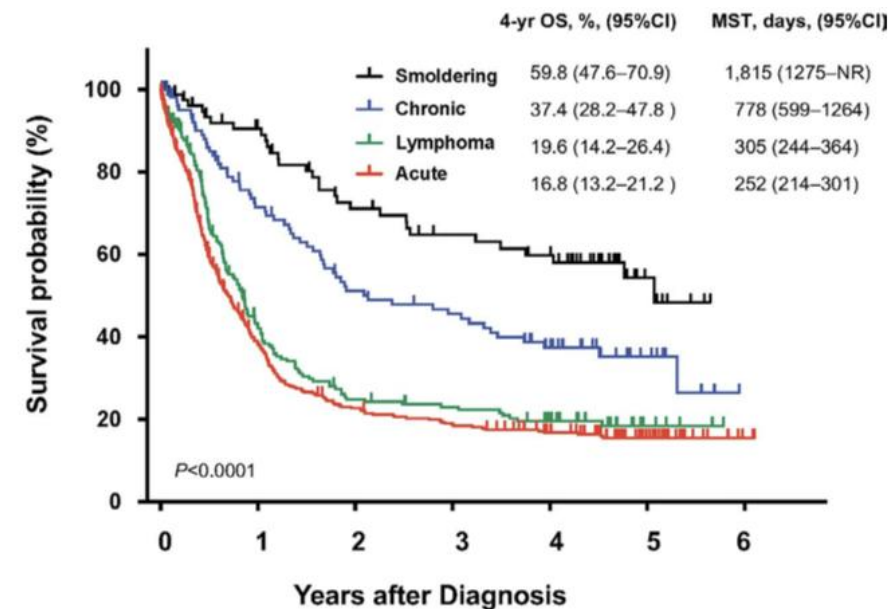


Prognosis of ATLL

- Median survivals: 6-8 months for acute, and 10-22 months for lymphomatous subtypes
- Allogeneic stem cell transplant (graft vs. lymphoma effect) may cure up to 40% of patients who reach this therapy (mostly from Japanese studies)

Japan:

N= 770 (Years 2010-2017)

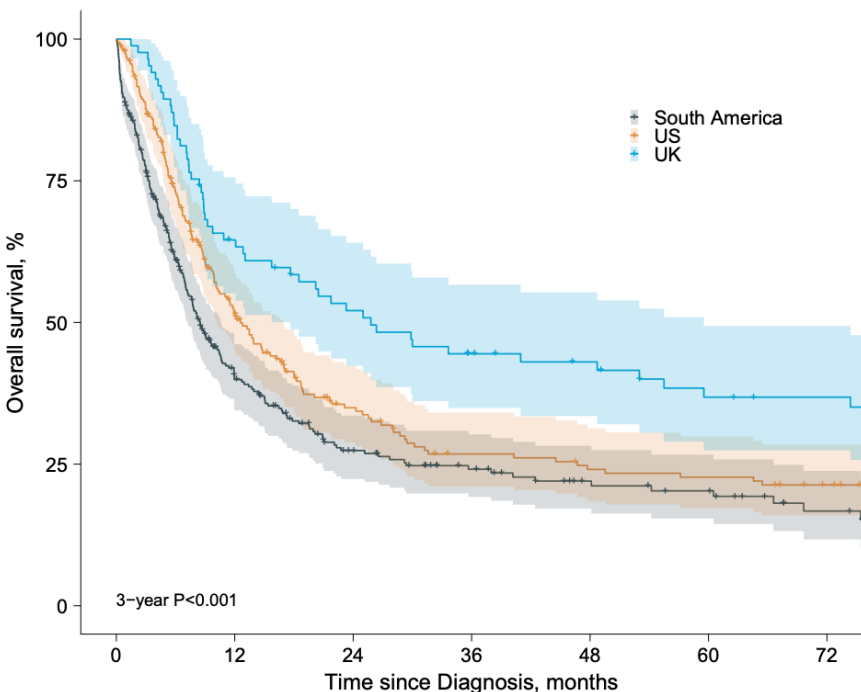


No. at risk						
Smoldering	81	63	47	40	36	10
Chronic	106	69	48	41	29	11
Lymphoma	192	70	41	35	25	6
Acute	391	131	76	62	47	20

Imaizumi et al. *Cancer Science* 2020

United States, United Kingdom, and South America

N= 607 patients (Years 2000-2023)



	Number at risk (number censored)						
South America	312 (0)	97 (42)	54 (57)	38 (67)	26 (76)	22 (78)	12 (85)
US	230 (0)	101 (25)	57 (39)	40 (43)	35 (44)	33 (44)	27 (48)
UK	85 (0)	53 (2)	41 (4)	33 (6)	29 (9)	23 (11)	21 (13)

Valcarcel et al. ASH 2025 Poster, *Br J Haematol* 2026

ATLL Genetic Landscape

Mutations affecting TCR and/or NF-κB signaling

GENE	Japan	U.S./LATAM
PLCG1	36% 14% R48W	27% 14% R48W
PRKCB	33% 26% D427N	11% 10% D427N
CARD11	24%	11%
STAT3	21%	13%
VAV1	18%	13%
NOTCH1	15%	10%
IRF4	14% 7% K59R	10% 4% L70V
CSNK1A1*	5%	1%
CBLB*	3% (deletion 7%)	9% (deletion 13%) *
RHOA	8%	7%

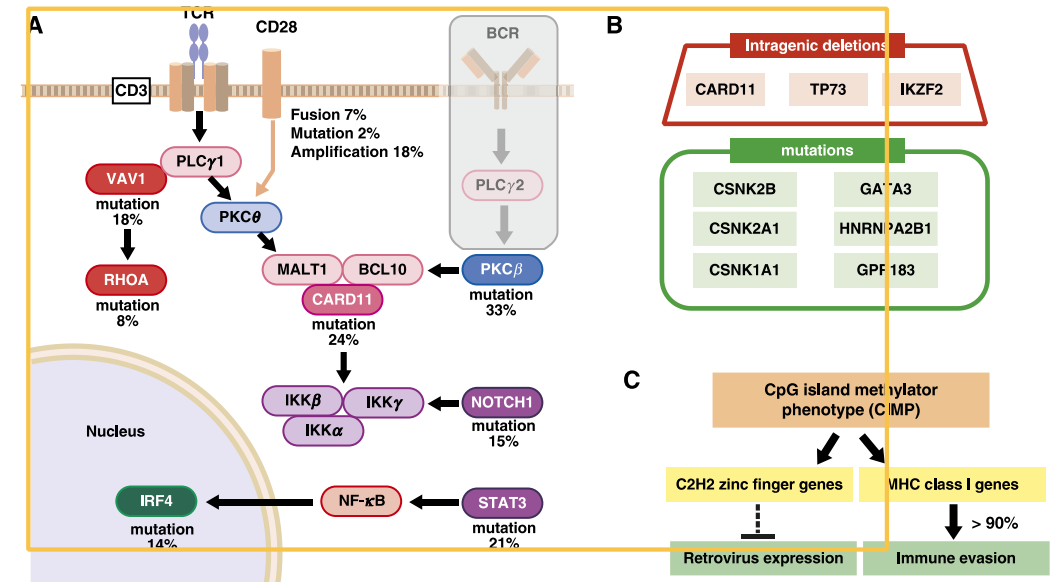
Mutations affecting G protein-coupled receptors

CCR4*	29% 14% Y331X	16% 10% Y331X
CCR7	11%	8%

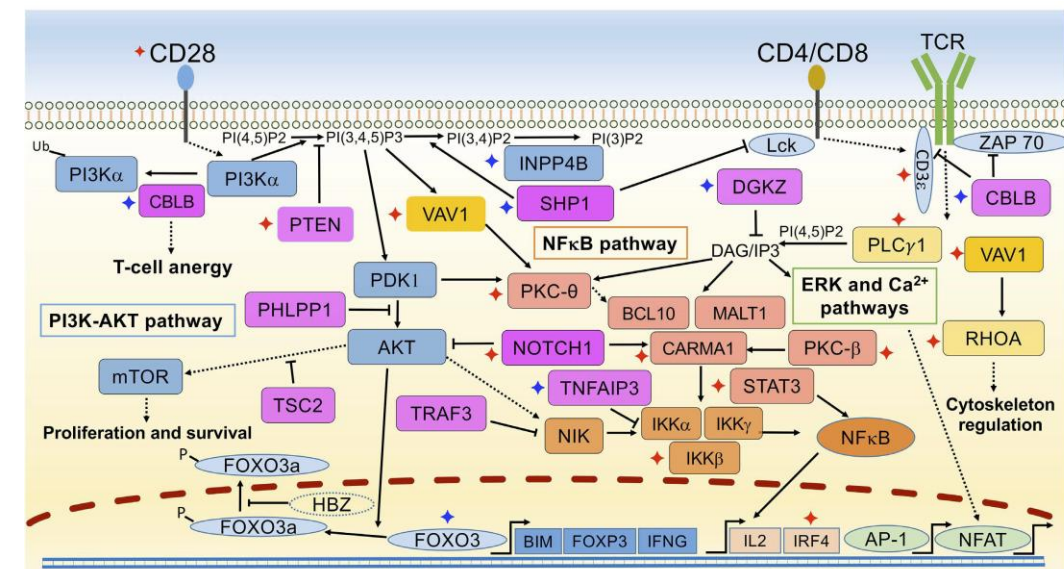
Other mutations/alterations

	Japan	U.S./LATAM
CDKN2A deletion	27%	24%
TP53 mutations / deletions	18% / 23%	17% / 12%
GATA3 mutations / deletions	11% / 14%	12% / 13%
FOXO3* mutations / deletions	<1% / 14%	10% 6% R177W / 10%
ANKRD11* mutations / deletions	10% / <1%	16% / 6%
Structural variations in PDL-1	27%	---

Kataoka et al. *Nature Genetics* 2015



Myers et al. *Haematologica* 2024



Treatment Options for ATLL

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

T-Cell Lymphomas

Version 2.2026 — February 13, 2026

INITIAL THERAPY

Preferred (alphabetical order)

- Clinical trial
- CHP (Cyclophosphamide/Doxorubicin/Prednisone) + Brentuximab vedotin for CD30+ cases
- CHOP (Cyclophosphamide/Doxorubicin/Vincristine/Prednisone) + Mogamulizumab-kpkc^{d,e} (no intention to proceed to transplant)
- Dose-adjusted EPOCH (Etoposide/Prednisone/Vincristine/Cyclophosphamide/Doxorubicin)
- Interferon/Zidovudine^f (acute, chronic, and symptomatic smoldering subtypes)

Other Recommended (alphabetical order)

- CHOEP (Cyclophosphamide/Doxorubicin/Vincristine/Etoposide/Prednisone)
- HyperCVAD (Cyclophosphamide/Vincristine/Doxorubicin/Dexamethasone) alternating with High-Dose Methotrexate/Cytarabine

Useful in Certain Circumstances

- CHOP (Cyclophosphamide/Doxorubicin/Vincristine/Prednisone) (unable to tolerate intensive regimen or non-CD30 expressing ATLL)

SECOND-LINE THERAPY OR SUBSEQUENT THERAPY

Preferred (alphabetical order)

- Clinical trial
- Single agents
 - Brentuximab vedotin for CD30+ cases
 - Lenalidomide^g
 - Mogamulizumab-kpkc^{d,e,g}
- Combination regimens
 - DHA (Dexamethasone/Cytarabine) + platinum (Carboplatin, Cisplatin, or Oxaliplatin)
 - ESHA (Etoposide/Methylprednisolone/Cytarabine) + platinum (Cisplatin or Oxaliplatin)
 - GDP (Gemcitabine/Dexamethasone/Cisplatin)
 - GemOx (Gemcitabine/Oxaliplatin)
 - GVD (Gemcitabine/Vinorelbine/Liposomal Doxorubicin)
 - ICE (Ifosfamide/Carboplatin/Etoposide)
 - Interferon/Zidovudine^f (acute, chronic, and symptomatic smoldering subtypes)

Alternative (alphabetical order)

- Single agents
 - Alemtuzumab^h
 - Arsenic trioxide
 - Belinostat
 - Bendamustine
 - Gemcitabine
 - Pralatrexate
 - RT in selected cases with localized, symptomatic diseaseⁱ

Available First line Treatment Options for ATLL in U.S.A

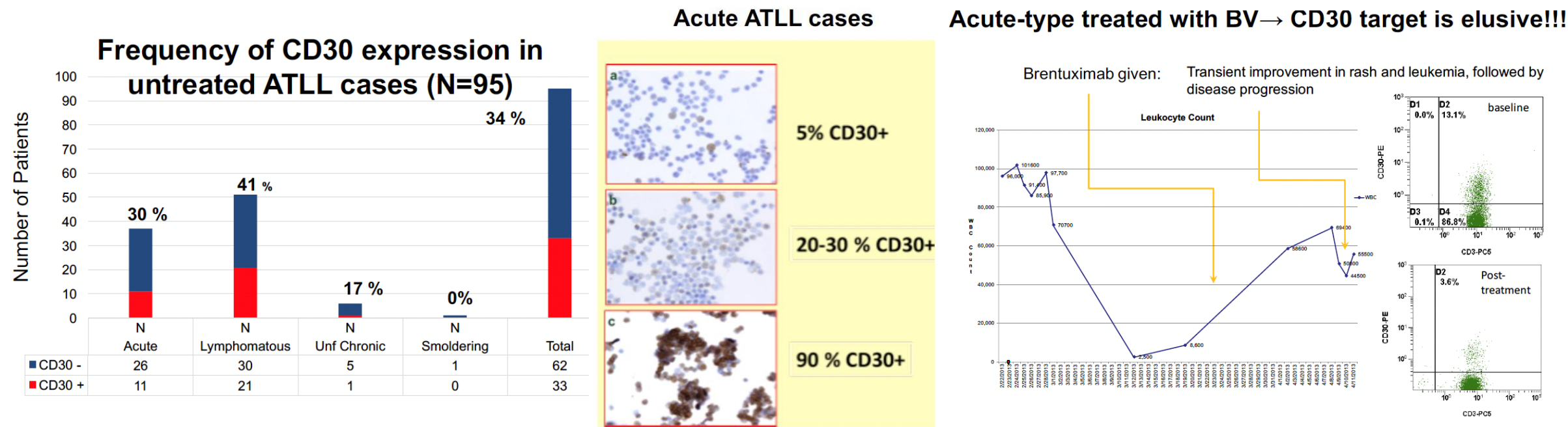
Regimen:	N	Overall response (ORR)	Complete response (CR)	Survival
○ EPOCH-bortezomib-raltegravir (Ratner, <i>Blood Cancer</i> 2016)	18	68%	17%	PFS 5.8 mo.
○ EPOCH-followed by AZT-interferon (Ratner, <i>PLoS One</i> 2009)	19	91% in evaluable	17%	PFS 5 mo.
○ EPOCH-lenalidomide (Ratner et al.)	Pending results: trial stopped early			
○ Miami retrospective study (Malpica et al. <i>Blood Adv</i> 2018)				
• EPOCH-based/CHOEP	33	79%	27%	---
• CHOP/CHOP-like	32	75%	34%	---
○ LATAM retrospective study (Malpica, <i>Lancet Haematol</i> 2025)				
➤ EPOCH/CHOEP	71	63%* $p=0.0009$	41%	3-yr OS 20%
• CHOP	125	38%	17%	3-yr OS 18%

Japanese regimens:	N	ORR	CR rate	Survival
➤ CHOP-14 + mogamulizumab (anti-CCR4 ab) in “elderly” (Yoshimitsu et al. <i>Blood</i> 2025)	92	92%	65%	PFS 36%
○ CHOP-14 vs. VCAP-AMP- VECF (Tsukasaki et al. <i>JCO</i> 2007)				3-yr OS
• VCAP-AMP-VECF	57	40%	40%* ($p = 0.20$)	24% ($p = 0.085$)
• CHOP-14	61	25%	25%	13%
○ VCAP-AMP-VECF +/- moga (Ishida et al. <i>Br J Haematol</i> 2015)				
• Mogamulizumab-VCAP-AMP-VECF	29	86%	52%*	PFS 8.5 mo
• VCAP-AMP-VECF	24	75%	33%	PFS 6.3 mo

Brentuximab (BV) (anti-CD30 ab-MMAE)-based chemotherapy

Regimen	N	ORR	CR rate	Survival
• BV-CHP vs. CHOP (ECHELON-2 Horwitz et al. <i>The Lancet</i> 2019)	7	?	?	?
• BV-CHEP (Dittus et al. ASH 2024, <i>Br J Haematol</i> 2025): CD30 expression not required (44% patients were CD30+)	16	87.5%	62.5%	PFS 7 mo. OS 12 mo.
➤ BV-CHEP or BV-CHP: Naveau et al. HTLV-1 London 2024 (Retrospective study, single institution)	20	65%	50%	PFS 9 mo.

University of Miami Experience (Malpica et al. ASH 20170)



Other Available Treatment Options for ATLL in the U.S.A

Combination Chemotherapy

Regimen	Comments
○ <i>Hyper cVAD as first line (case report)</i>	2 patients had CR
➤ <i>Salvage, platinum-based (i.e. DHAP, GDP, GemOx, ICE)</i>	No clear evidence Recommend as bridge in transplant eligible patients

Biological or single agents

Regimen	N	ORR	CR rate	Survival
➤ <i>brentuximab (BV)</i>	Clinically active!			
➤ <i>lenalidomide</i> in R/R ATLL - Ishida et al. <i>JCO</i> 2016 - Phillips et al. <i>Int J Blood Res Disord</i> 2015	26 4	42% (11) 0%	15% (4) 0%	PFS 3.8 mo., OS 20 mo.
➤ <i>mogamulizumab</i> in R/R ATLL - Ishida et al. <i>JCO</i> 2012 - Phillips et al. <i>Haematologica</i> 2009	26 47	50% 11% (vs 0% investigator's choice	29% 2% (1)	PFS 5.2 mo. , OS 3.7 mo. PFS 0.9 mo.
○ <i>HDAC inhibitors (belinostat, romidepsin)</i>	Clinically active! I do not recommend it without outside of a clinical trial or without adding anti-antiviral			
○ <i>alemtuzumab</i> (anti-CD52 ab) in R/R ATLL: Sharma et al. <i>Clin Cancer Res</i> 2017	29	52% (no effect in lymphomatous)	21%	PFS: 2 mo.
○ <i>pralatrexate</i> in R/R ATLL: Lunning et al. <i>Blood</i> 2012	21	19% in evaluable (4)	6% (1)	

Zidovudine (AZT) plus interferon (IFN α)

Miami Experience: Malpica et al. *Blood Adv.* 2018

- AZT-IFN α can be efficacious in aggressive leukemic ATLL with longer progression-free survival (PFS) as compared to chemotherapy in patients who achieve complete response (CR)

CR rates after first line:

Chemotherapy:

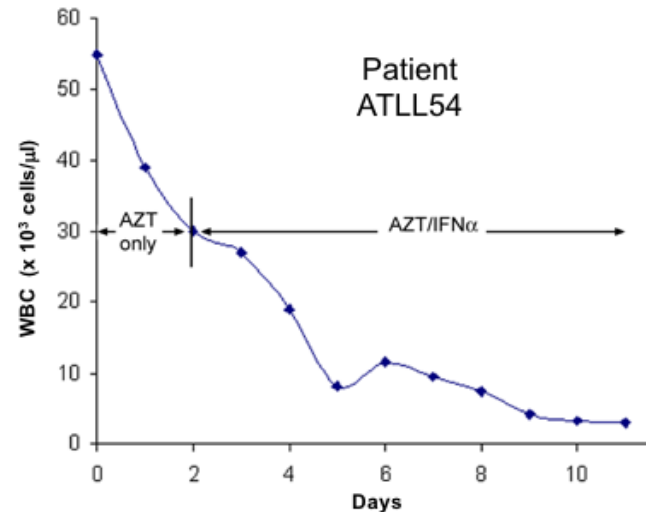
- Acute: 6/18= 33%
- Lymphomatous: 18/50= 36%

AZT-IFN α :

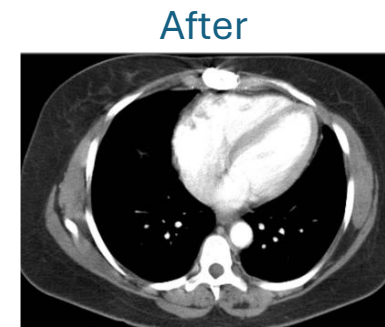
- Acute: 10/42= 24%
- Lymphomatous: 1/10= 10%

- AZT-IFN α + AsO₃
- Kchour et al. *Blood* 2009 – chronic ATLL: 10/10 patients (100%) had CR
- Hermine et al. *Hematol J.* 2004- aggressive ATLL: 7 patients (1 CR, 2PR)

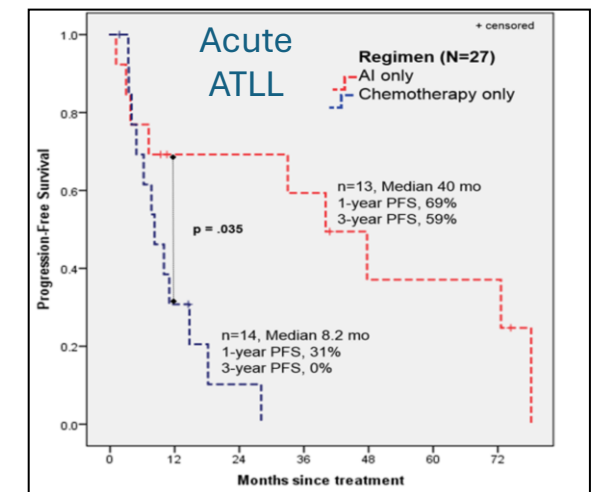
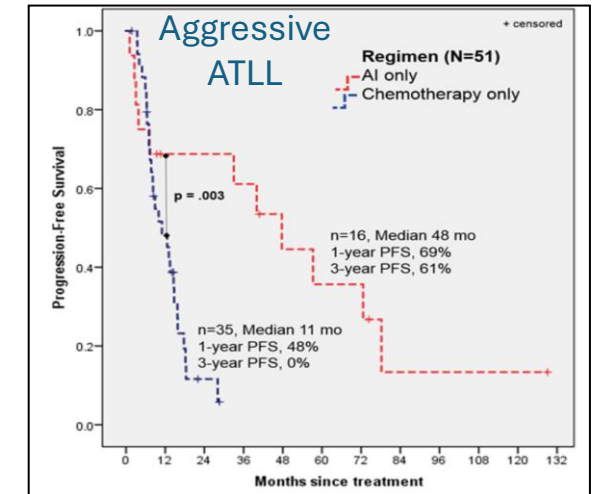
CR in acute ATLL presenting with widespread disease and hypercalcemia after AZT-IFN α



PFS:
4 years



PFS after first CR

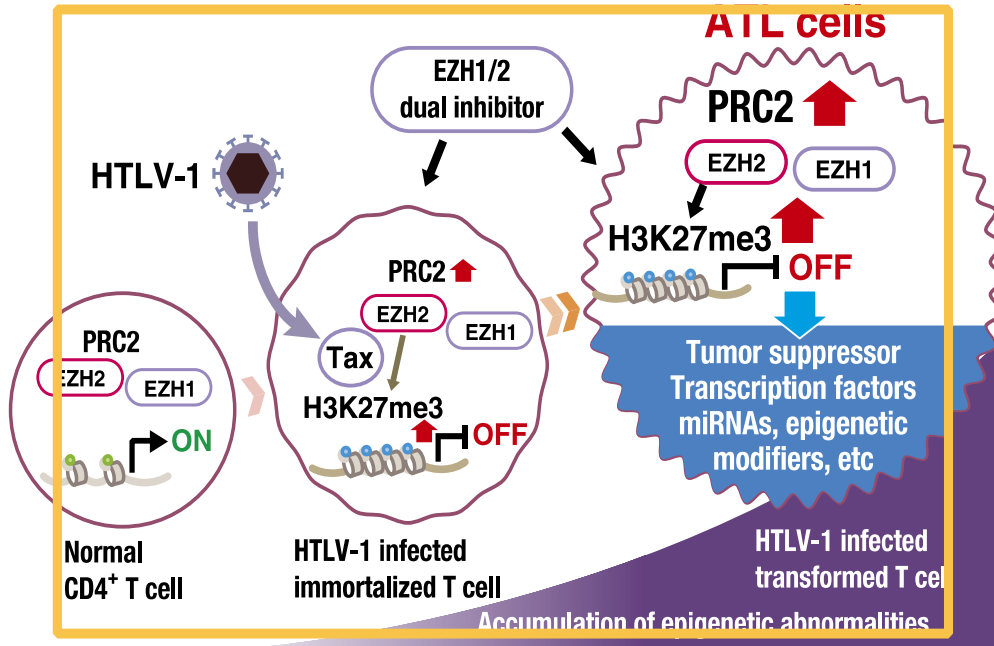


Epigenetics of ATLL

Epigenetic Landscape of ATLL

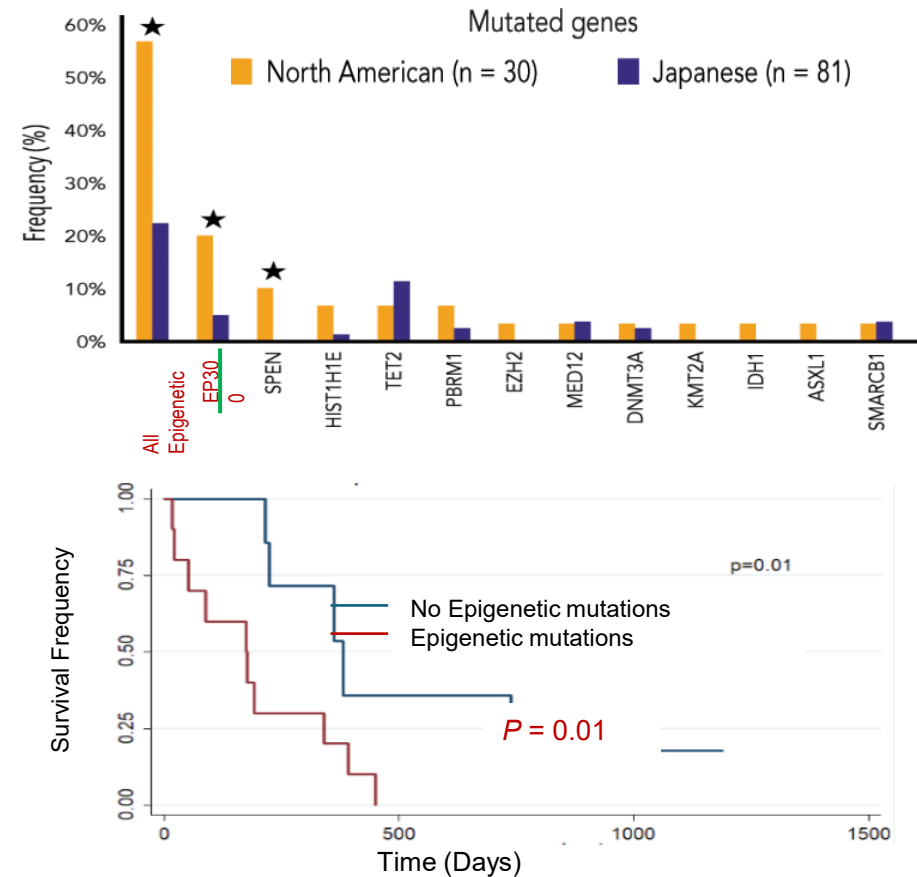
(Watanabe, *Blood* 2017)

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



Epigenetic gene mutations in North American (NA) ATLL (Shah al. *Blood* 2018)

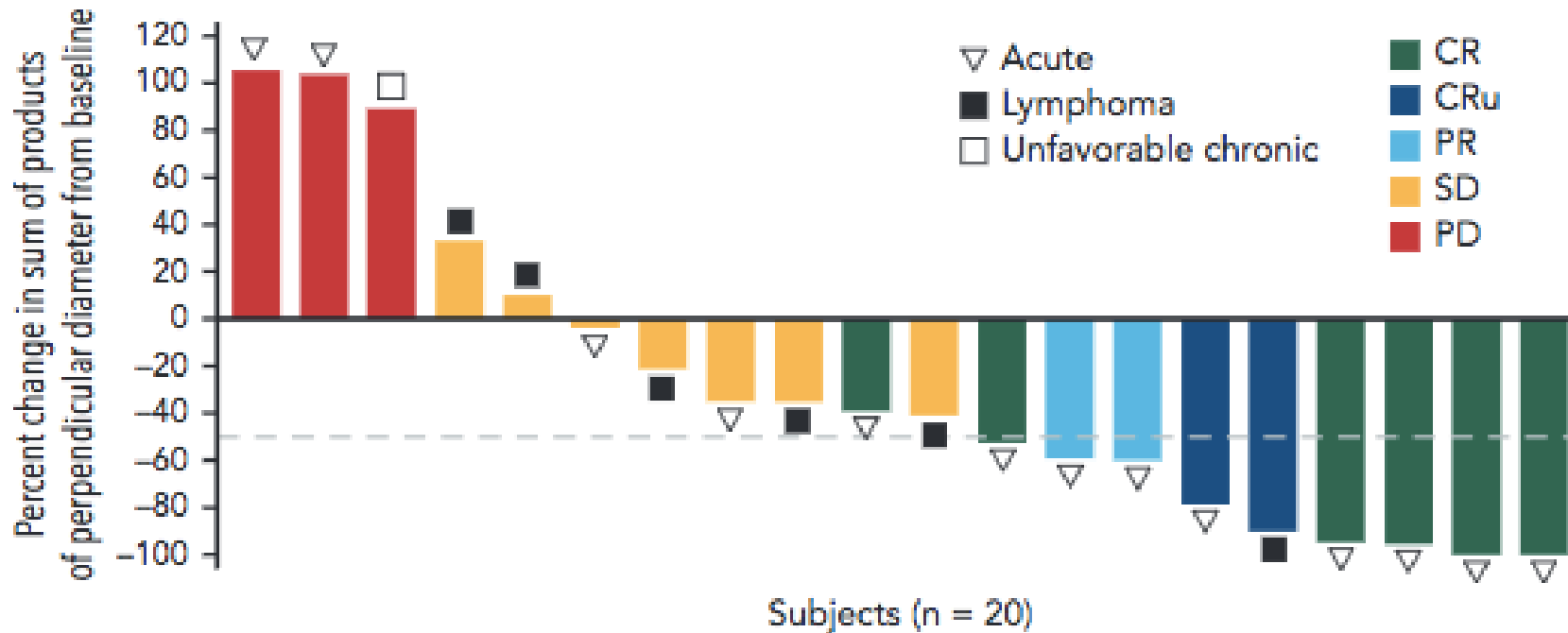
- *Techniques:* Targeted deep next-generation sequencing of NA-ATLL samples (n=30) compared to Japan WES (n=83)
- *Findings:* More frequent epigenetic mutations in NA-ATLL



Targeting ATLL using EZH1/2 inhibitor

Phase 2 trial of valemestostat for R/R ATLL (Izutsu et al. *Blood* 2023)

- ORR 46% (CR 20%)
- Median DOR: not reached
- *Valemestostat* approved in Japan on Sept. 2022 for R/R ATLL



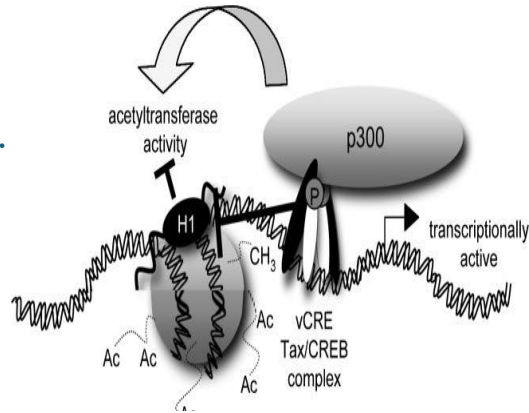
Targeting HTLV-1/ATLL Using Histone Deacetylase Inhibitors (HDACi)

HTLV-1 promoter is regulated by HDACs and by HBZ

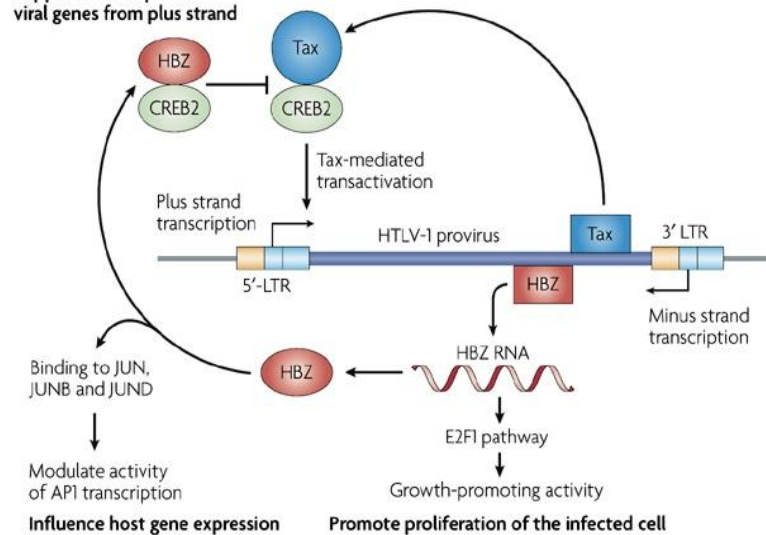
HDAC inhibitors induce **Tax** and dose-dependent caspase-mediated apoptosis ($\uparrow$ **BIM**), and block **HBZ** protein expression

ATLL84c (ATLL patient derived line)

Konesky et al.
JVI 2006

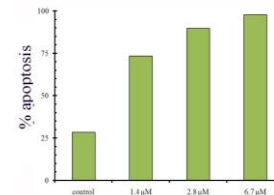


Suppress transcription of viral genes from plus strand

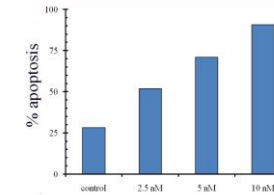


Matsuoka et al. *Nat Rev Cancer* 2007

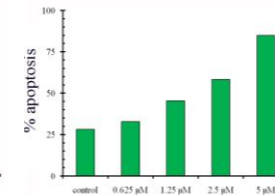
valproic acid



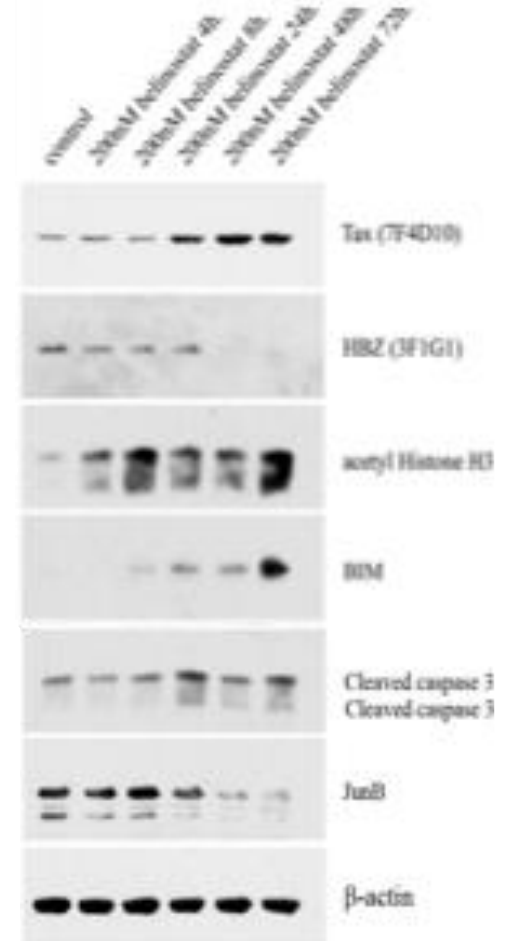
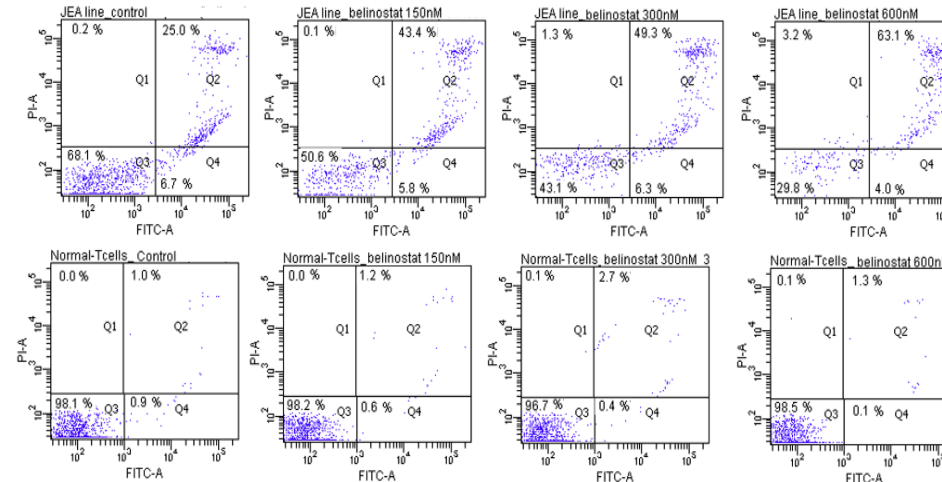
LBH-589
(panabinoostat)



SAHA
(vorinostat)



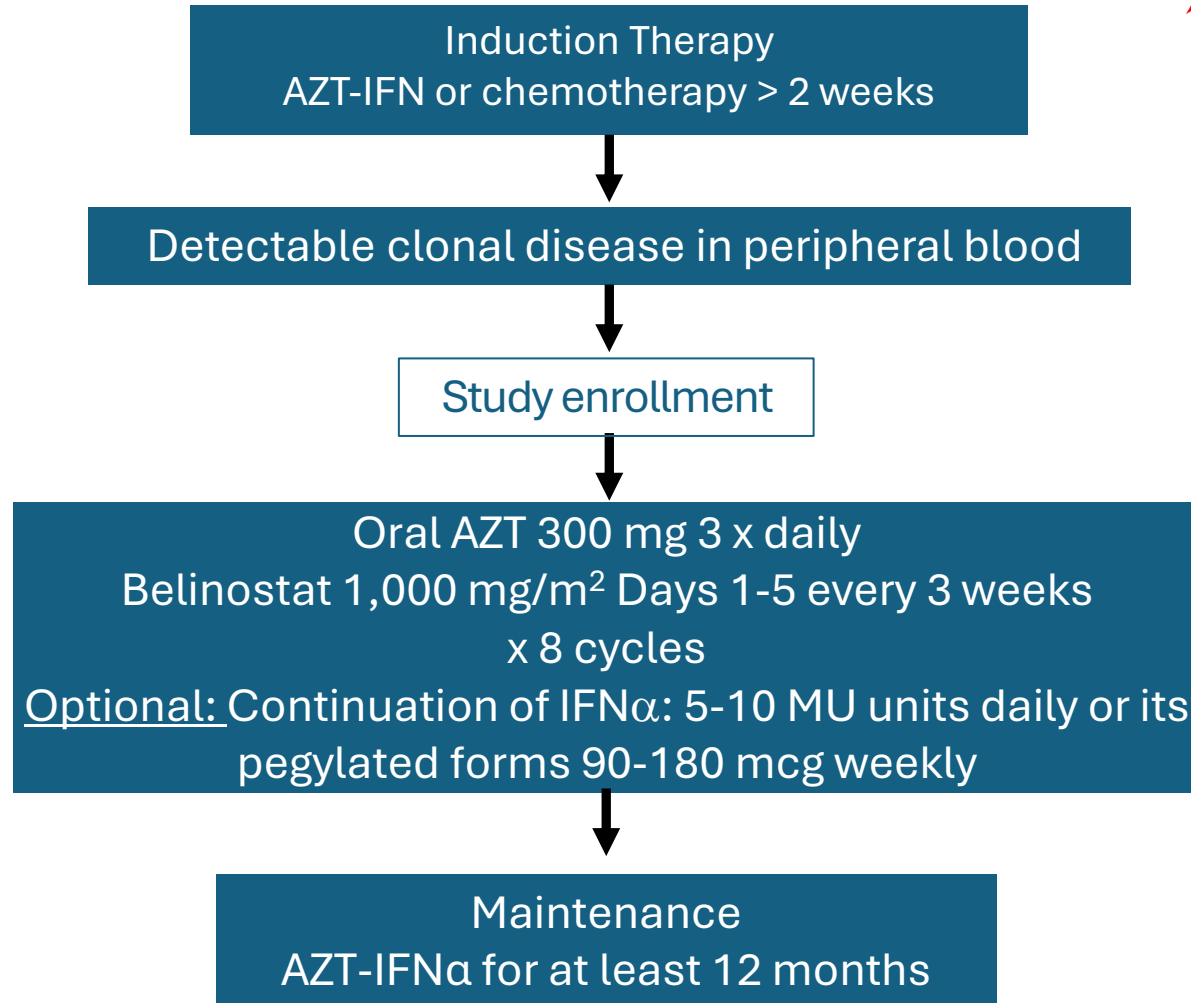
belinostat 150-600 nM



Ramos lab

Safety and Efficacy of AZT/IFN α with Belinostat (AI-BEL) for ATLL

(Clinicaltrials.gov NCT02737046)



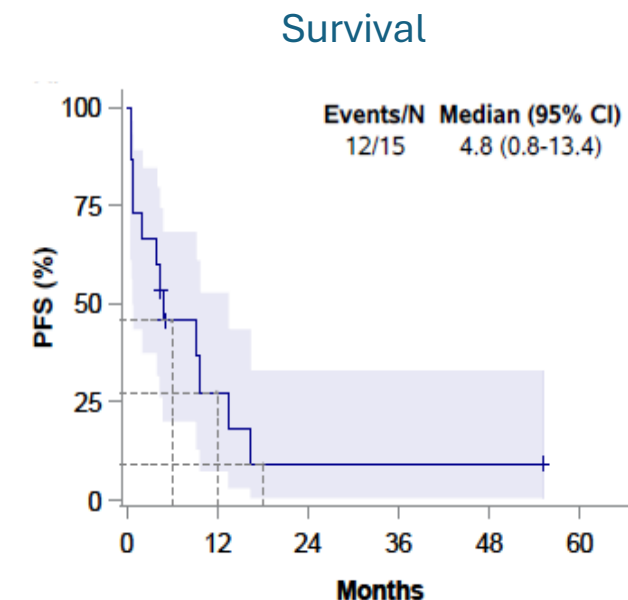
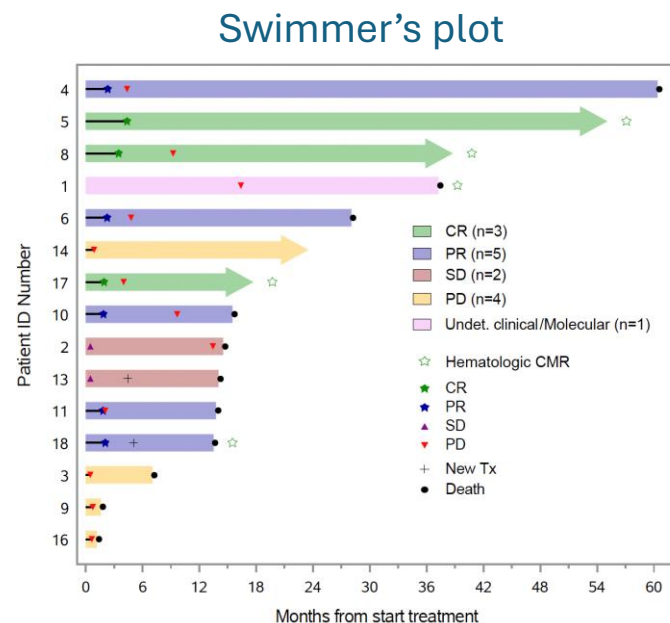
➤ **Hypothesis:** HDAC inhibition will reactivate HTLV-1 in ATLL/host infected cells in patients treated with AZT-IFN α to elicit anti-HTLV-1/ATLL immune responses!

- *Eligibility:* Newly diagnosed or relapsed ATLL with active disease in peripheral blood after starting AI, steroids, or chemotherapy
- *Primary objectives:*
 - Safety
 - Complete molecular response (CMR)
- *Secondary objectives:*
 - Clinical responses and survival rates
 - Immunologic responses (i.e. CTL)
 - Effect on HTLV-1 proviral loads and clonal abundance
 - Study molecular effects in vivo

AI-BEL in Patients with Acute ATLL: Final Results (Ramos et al. ASH2025)

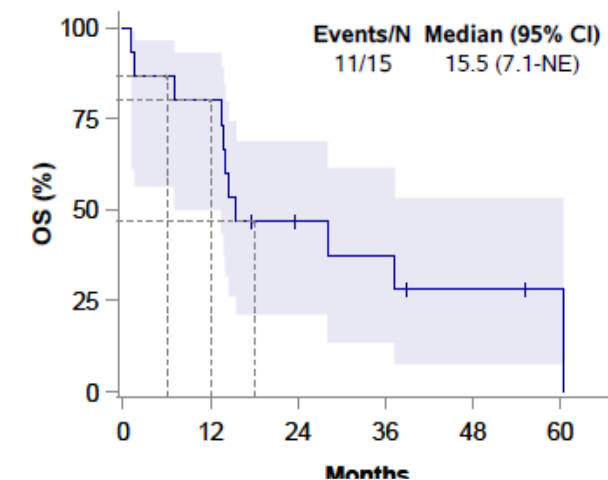
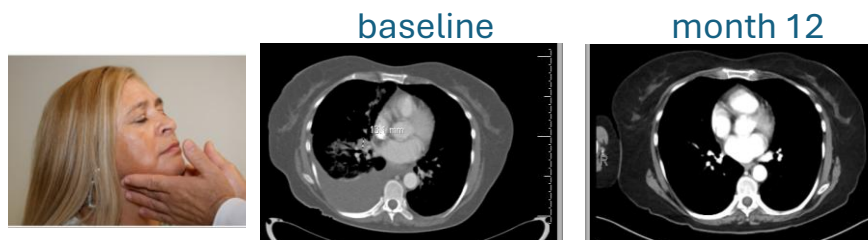
SAFETY (N=15)	N (%)
Grade 3 or 4 events	11 (73)
○ Neutropenia	9 (60)
• Febrile neutropenia	1 (7)
• Prolonged agranulocytosis	1 (7)
○ Thrombocytopenia	7 (47)
○ Anemia	6 (40)
Dose reduction or discontinuation	9 (60)

EFFICACY	N (%)
Overall response (N=14 evaluable)	8 (57)
○ Complete response (CR)	3 (21)
○ Partial response (PR)	5 (36)
○ Stable disease (SD)	2 (14)
Clinical benefit (N=15 evaluable)	11 (73)
○ Complete molecular response (CMR) in blood compartment	3 (20)



Patient 5

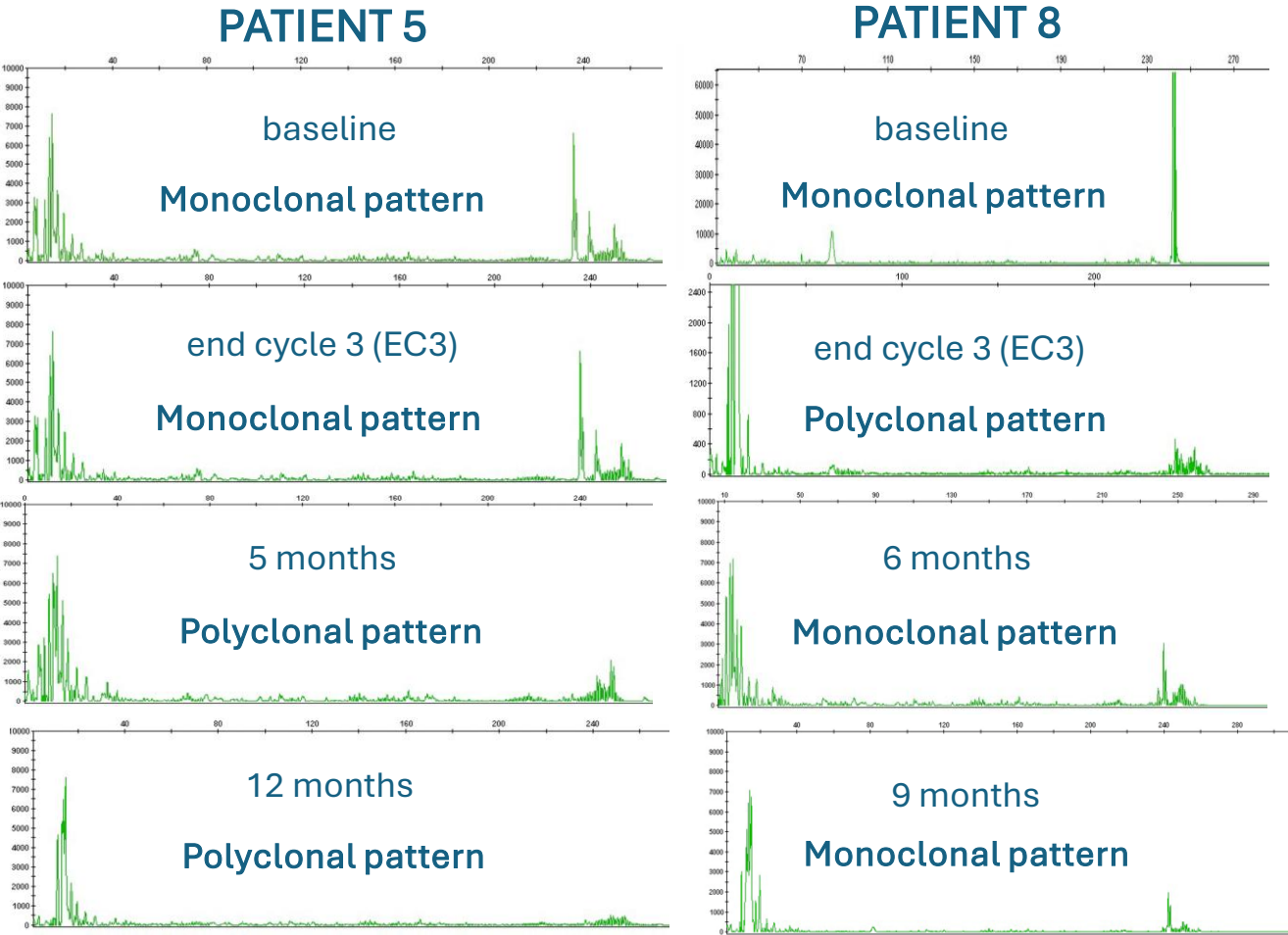
- AZT-IFN x 3 wk. followed by AI-BEL (stopped after cycle 3 due hematologic toxicity)
- **Spontaneous CMR after Month 5**
- **Progression-free > 5 years!**



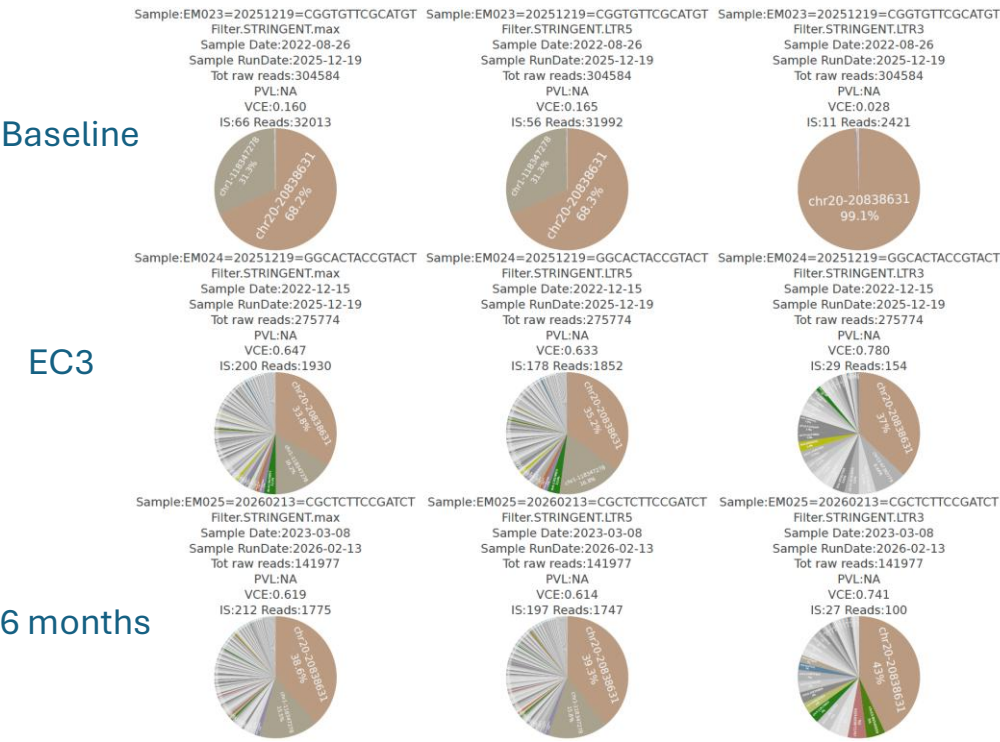
Telemundo: <https://www.telemundo51.com/noticias/local/sylvester-brinda-esperanza-a-pacientes-con-canceres-de-sangre-agresivos/2705284/>

Molecular Responses after AI-BEL

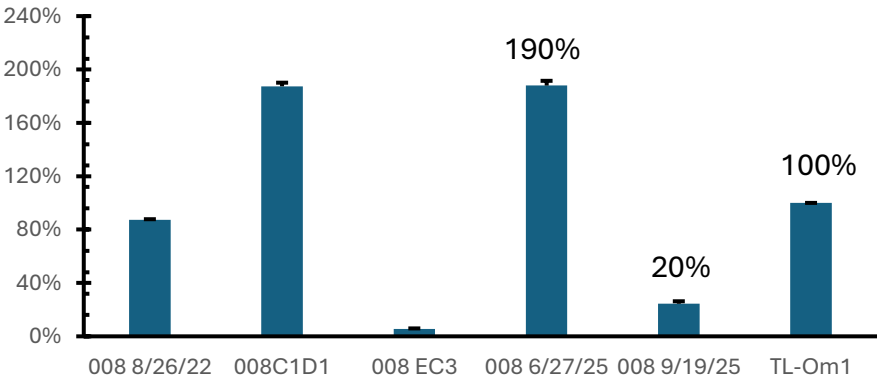
Multiplex PCR for TCR- γ (PBMCs)



PATIENT 8: HTLV-1 integration site by NGS

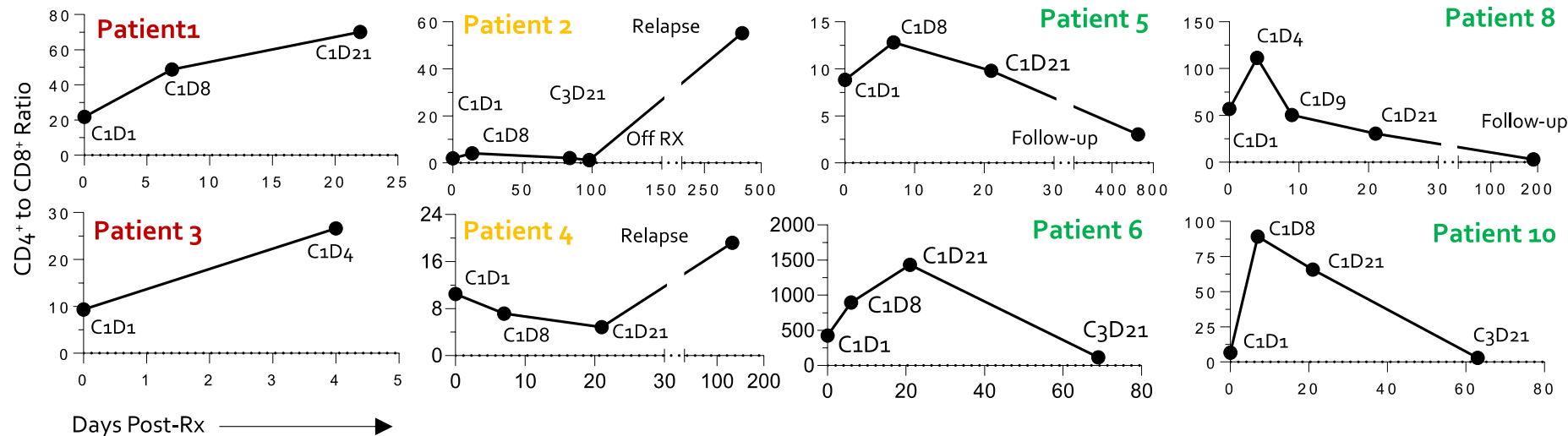


HTLV-1 proviral load by digital droplet PCR



Immune Responses after AI-BEL Trial: Serially Collected PBMCs

Clinical Response is associated with expansion of CD8⁺ compartment



- Significant population of exhausted CD8⁺ T cells (PD-1⁺ TIGIT⁺ TOX⁺) noted in all baseline samples
- Rise of unique CD8⁺ T-cell subsets in responders

Patient	Age/Gender	Trial Response
1	32/F	Early Flare
2	67/M	Maintained Partial Response
3	60/M	Progressive Disease
4	45/F	Partial Response
5	55/F	Complete Molecular Response
6	71/M	Near Complete Response
8	47/M	Complete Molecular Response
9	75/F	Progressive Disease
10	36/M	Near Complete Response

Emerging Investigational Approaches for ATLL in U.S.A

○ Chemotherapy trials

- *Study of Mogamulizumab With DA-EPOCH or CHOEP in Patients With Aggressive T-cell Lymphoma* (ClinicalTrials.gov NCT05996185) (Yale University)

○ Cell therapy and CAR T cell efforts

- *Anti CD70 (allogeneic) (CTX130) for R/R for T-cell Lymphoma* [ASH 2025]:
 - N= 6 ATLL, ORR was 50% (2CR 1PR) Median PFS 2.5 mo.
- *Anti-CD5 for T-cell Lymphoma* (autologous) (LaQuisa et al. Blood 2024)
 - 1 ATLL patient had a PR
- *CD4CAR for CD4+ Leukemia and Lymphoma* (autologous) (University of Indiana)
- *Anti-CCR4* (autologous): NIH
- *Third-Party Natural Killer Cells and Mogamulizumab for the Treatment of Relapsed or Refractory CTCL or ATLL* (ClinicalTrials.gov NCT04848064) (OSU)

○ Post transplant studies

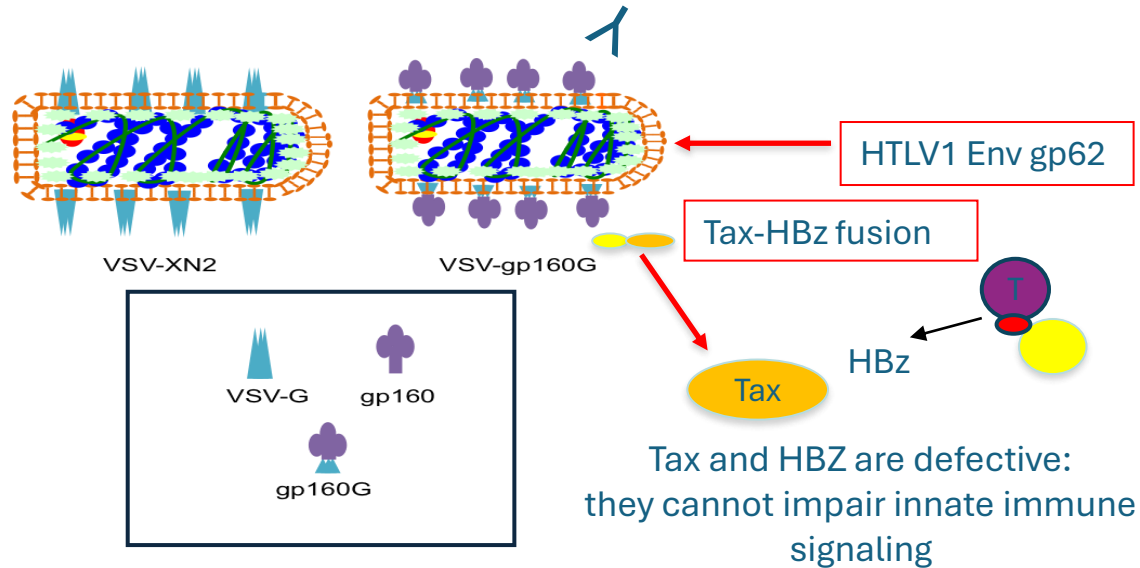
- *Ruxolitinib Maintenance Post-Hematopoietic Stem Cell Transplant T-Cell Lymphoma* (ClinicalTrials.gov NCT07356245) (OSU)

○ Therapies aimed at eradicating HTLV-1 infection

- *A Study of Mogamulizumab to Prevent ATLL in People With HTLV-1* (ClinicalTrials.gov NCT06698003) (MSK)
- *VSV-gp62-ΔHT HTLV-1* (Barber/Ramos): Phase 1 study in patients with HTLV-1/ATLL (pending activation)

Vesicular stomatitis virus (VSV)-based Vaccine for HTLV-1 (Barber lab)

HTLV1 VSV-based vaccine (preventive, therapeutic)



- The VSV envelope protein (G) has been replaced with the HTLV1 envelope protein (gp62)
- The recombinant virus also expresses the HTLV1 Tax and HBZ proteins

Objective:

- To generate neutralizing antibodies against gp62, to prevent syncytia formation and viral cell-cell spread
- To generate CTL activity to both Tax and HBZ, to clear infected cell populations

First-in-Human Vaccination Trial of VSV-gp62- Δ HT HTLV-1 to Eradicate HTLV-1 (Ramos) IND #: 29730

Enrollment of the first 3 patients (Dose escalation study)
Eligibility: Healthy HTLV-1 carriers, indolent ATLL, or prior ATLL

Prime shot (Day 1): 3-6 patients based on TLT
Starting at 1×10^6 TCID₅₀ (Intravenous)

1st Boost shot (Day 28): 3-6 patients based on TLT
Dose: 1×10^7 TCID₅₀ (Intravenous)

2nd Boost shot (Day 60): 3-6 patients based on TLT
Dose: 1×10^8 TCID₅₀ (Intravenous)

Primary Objectives

- To determine the safety
- To determine the recommended phase 2 dose (RP2D) based on treatment-limiting toxicity (TLT) during the first 60 days (after the 1st and 2nd vaccine doses)

Secondary Objectives

- To evaluate the pharmacokinetics
- To evaluate host antibody and cytotoxic T-cell (CTL) responses to HTLV-1 proteins (gp62, HBZ, and Tax) and vaccine's ability to induce neutralizing antibodies
- To evaluate overall survival at 1 year
- To evaluate HTLV-1 proviral loads longitudinally
- To evaluate treatment efficacy in patients who have indolent or chronic ATLL

Conclusions

- HTLV-1 related ATLL continues to carry a prognosis despite modern therapies
- Only allogeneic transplant offers a possible cure in some patients
- Combination chemotherapy has reached its limits
- Ab-dependent therapies (e.g. anti- CCR4, anti-CD30) may add efficacy, but their long-term impact is uncertain
- Biomarker-driven and ATLL subtype specific therapies are needed
- Potentially targetable alterations affecting TCR/NF- κ B signaling (PRKCB, PLCG1, IRF4) and PI3K signaling molecules could be exploited
- Novel biological drug approaches may include use:
 - Epigenetic drugs (e.g. EZH-1/2 inhibitors)
 - Judicious use of HDAC inhibitors + AZT-IFN α which can provoke sustained immune CD8 T-cell responses against ATLL
- Cell based therapies (CAR T-cells) have shown activity and should continue to be developed
- Novel immune-based (vaccine or cell-based) approaches that can target both ATLL and HTLV-1 infection are major goals!

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- Yi Zhou
- Isildhina Reis
- Paulo Pinheiro

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- Gregoire Lauvau (Albert Einstein College of Medicine, NY)
- Anne Van Den Broeke (University of Liège, Belgium)
- Anne-Sophie Reuter (University of Liège, Belgium)
- Alejandro A Gru, MD (Columbia University)
- Jaehyuk Choi, MD, PhD (UT Southwestern)
- Caroline Myers, MD (University of Pennsylvania)
- Graham Taylor (Imperial College, London, UK)
- Lee Ratner (Washington University)
- Eduardo Gotuzzo (Cayetano Heredia University, Lima, Peru)



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

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

Overview of current clinical trials data

Olivier Hermine
Necker Hospital, France



Adult T cell leukemia treatment perspectives in 2026

Olivier Hermine MD, PhD

Department of Hematology

INSERM 1163, Imagine Institute

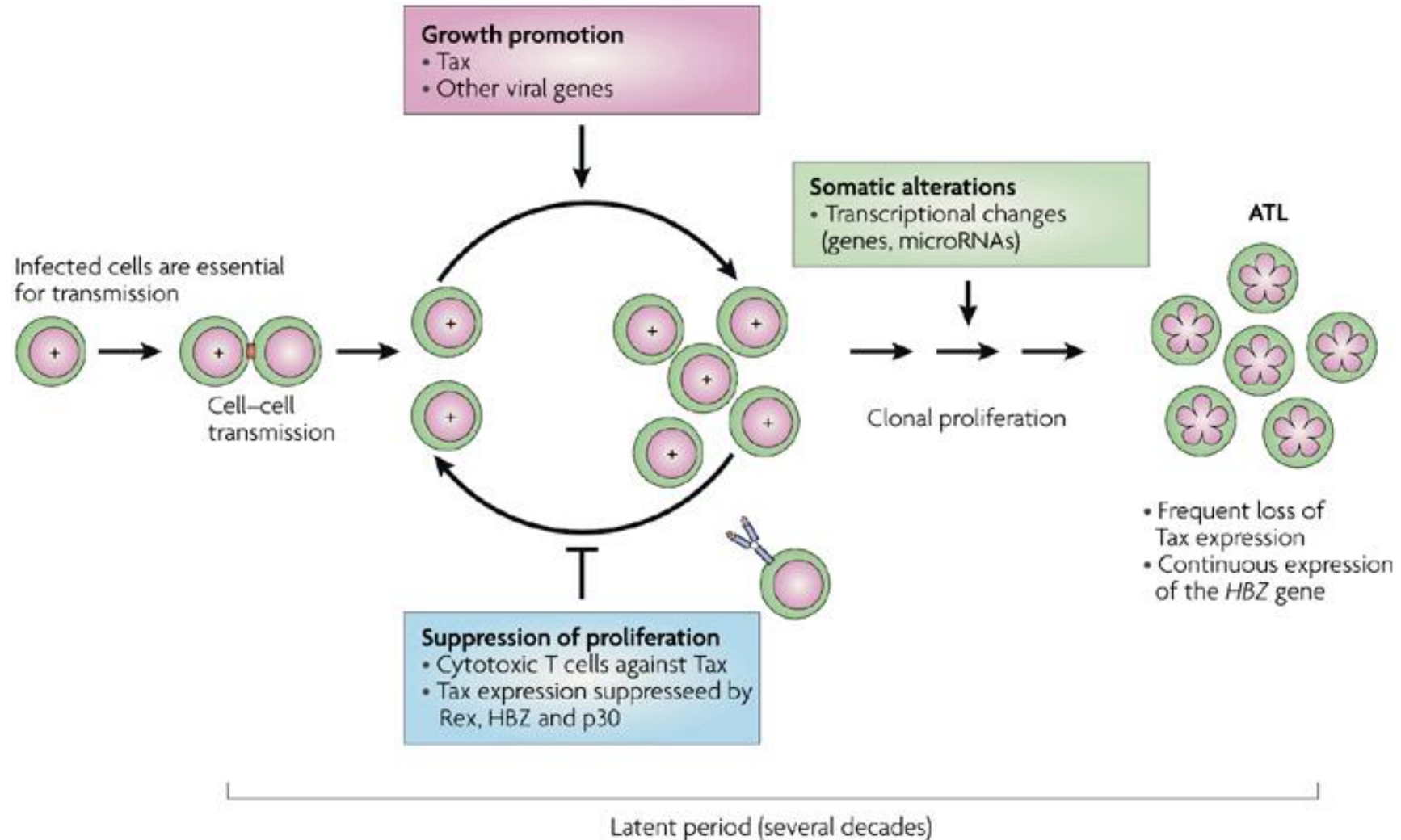
Necker Hospital, APHP, Paris cité University

Paris, France

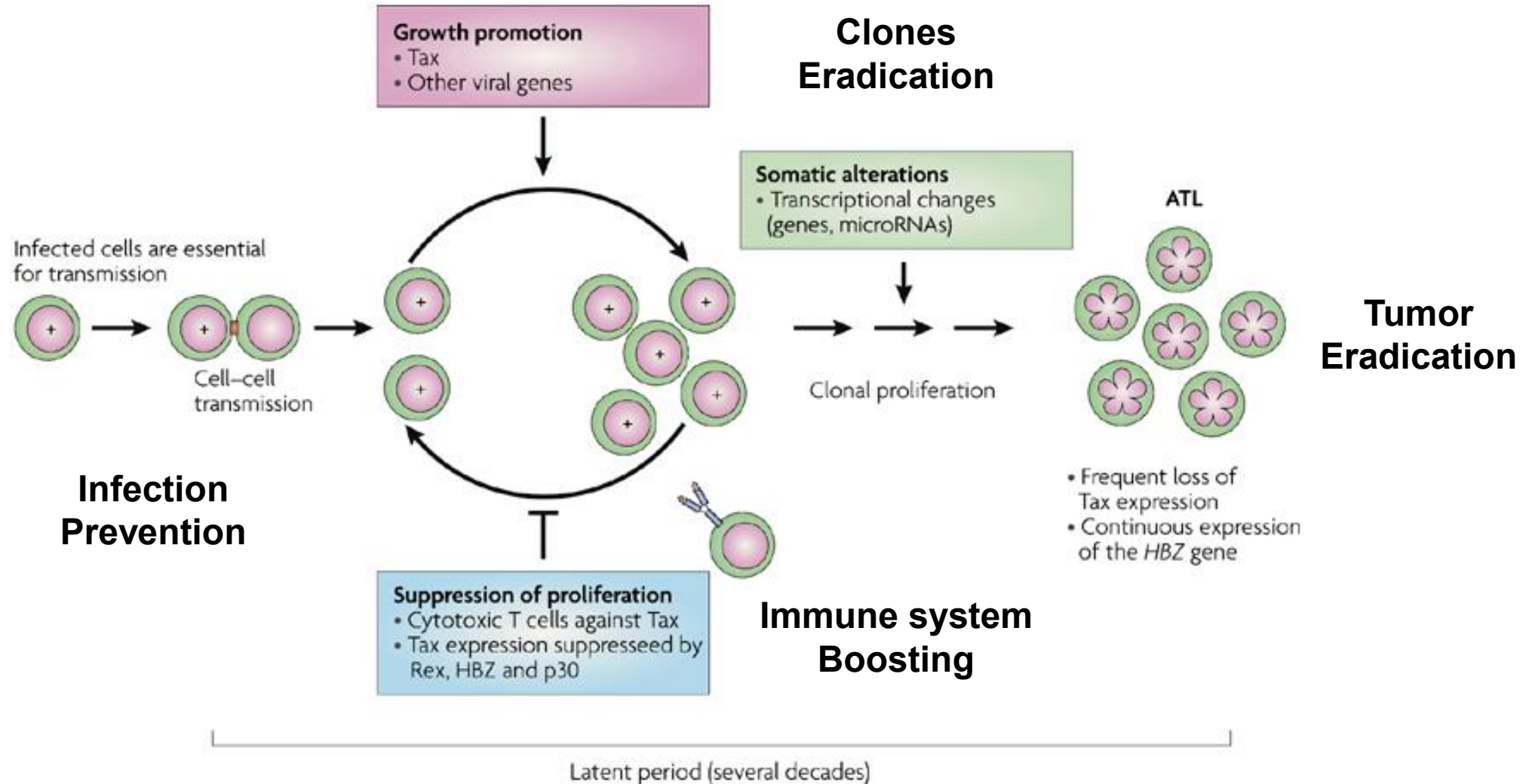


Physiopathology

ATL physiopathology



ATL physiopathology-Treatment



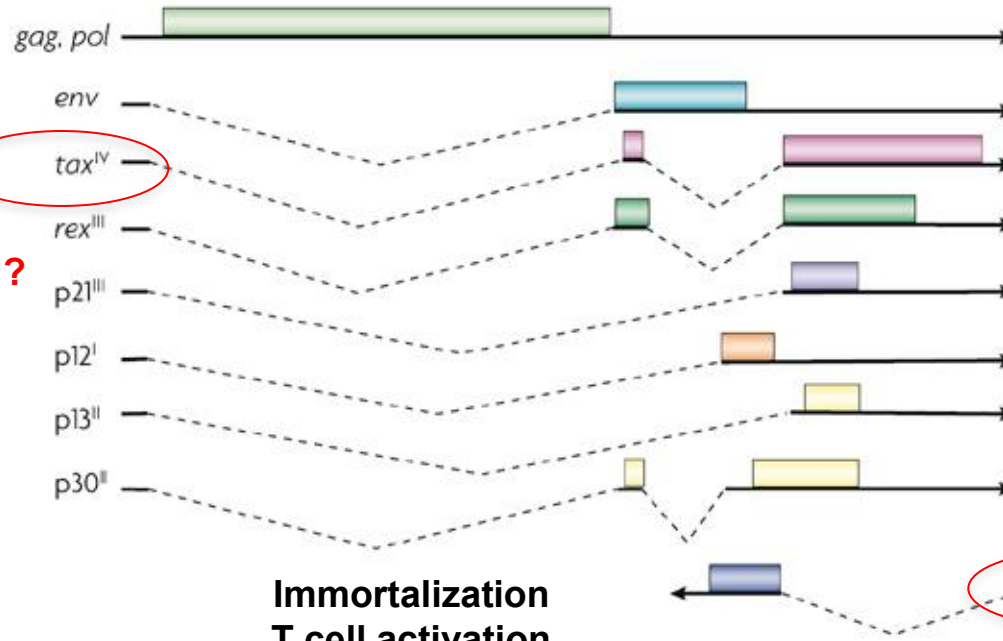
Virus Structure

Transcriptional silencing by DNA methylation of 5' LTR

Genetic changes in the tax gene



mRNAs



Proliferation
Antiapoptotic
Genetic stability
Epigenetic alterations

Expression ?

Role at the stage of transformation ?

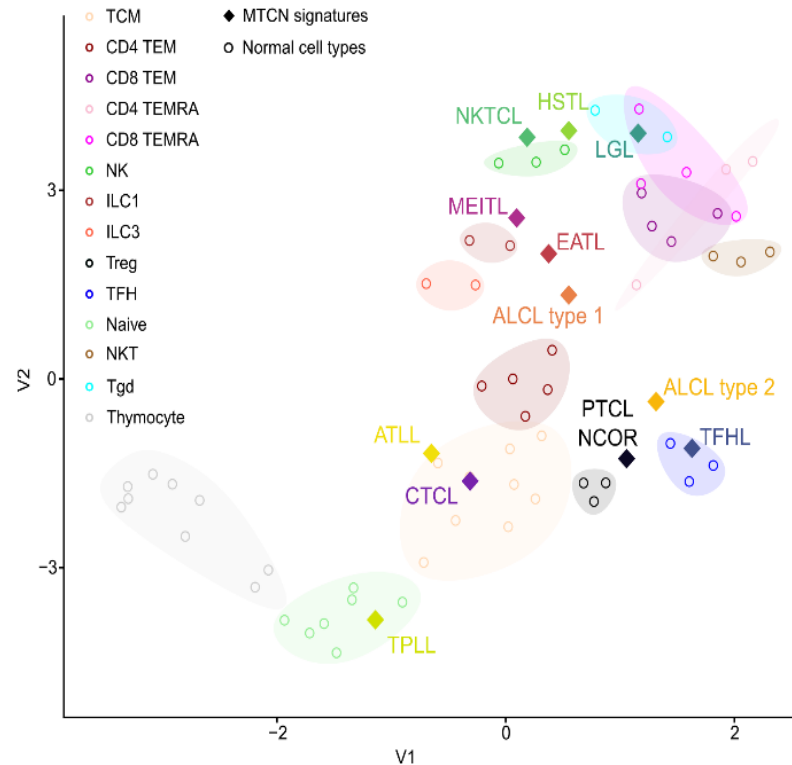
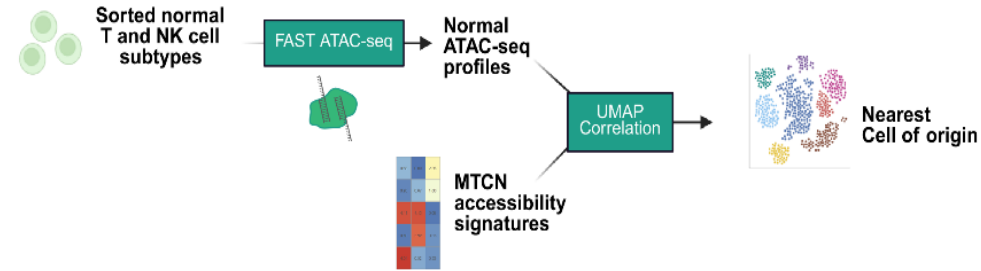
Immune Target ?

Immortalization
T cell activation
Oncogene integration

Expressed
Immune target ?

Nature Reviews | Cancer

Cell of Origin unknown (Epigenetic signature due to the virus ?)



Julia E, Bachy et al, unpublished
Do not post

Preventive Treatment
(after infection before transformation)

Risk of ATLL development in HTLV-1 carrier

A viral clonality evenness score to predict progression to adult T-cell leukaemia in asymptomatic carriers of human T-lymphotropic virus type 1 in Japan: a retrospective longitudinal cohort study

Snehal Dilip Karpe, Maria Artesi, Jérôme Wayet, Keith Durkin, Vincent Hahaut, Kaoru Uchamaru, Junya Makiyama, Masako Iwanaga, Atae Utsunomiya, P Martijn Kolijn, Anton W Langerak, Arsène Burny, Ambroise Marçais, Olivier Hermine, Toshiki Watanabe, Michel Georges, Anne Van den Broeke

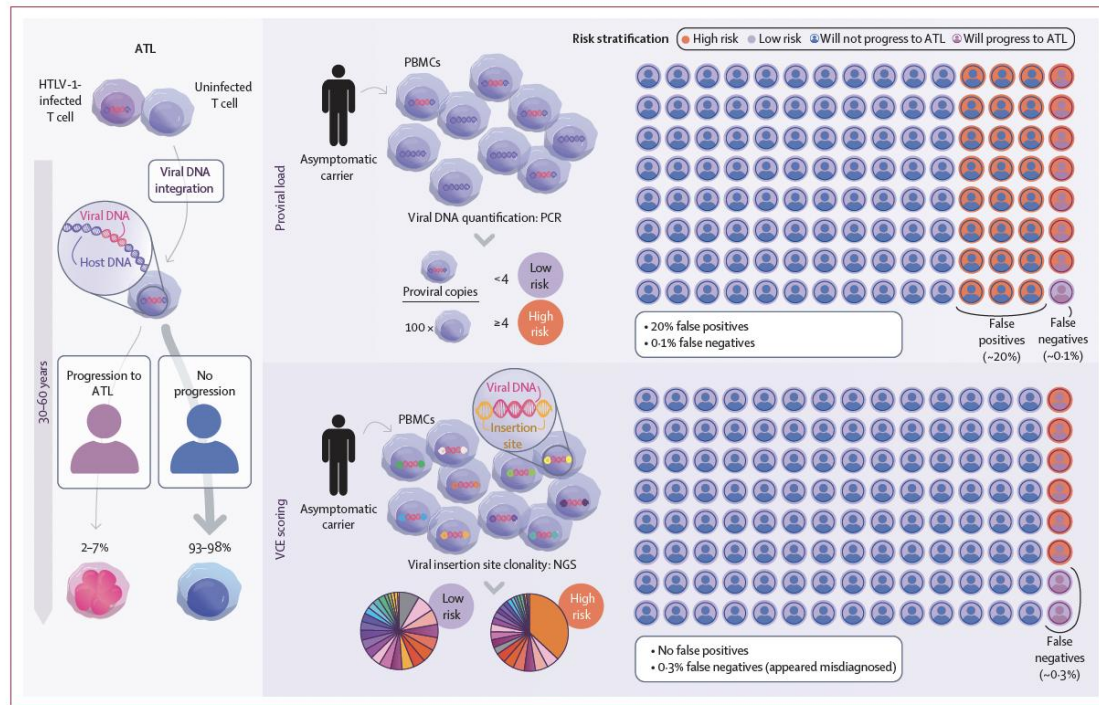


Figure 4: Risk stratification of asymptomatic HTLV-1 carriers on the basis of proviral load and VCE scoring
ATL=adult T-cell leukaemia/lymphoma. HTLV-1=human T-lymphotropic virus type 1. NGS=next-generation sequencing. PBMCs=peripheral blood mononuclear cells. VCE=viral clonality evenness.

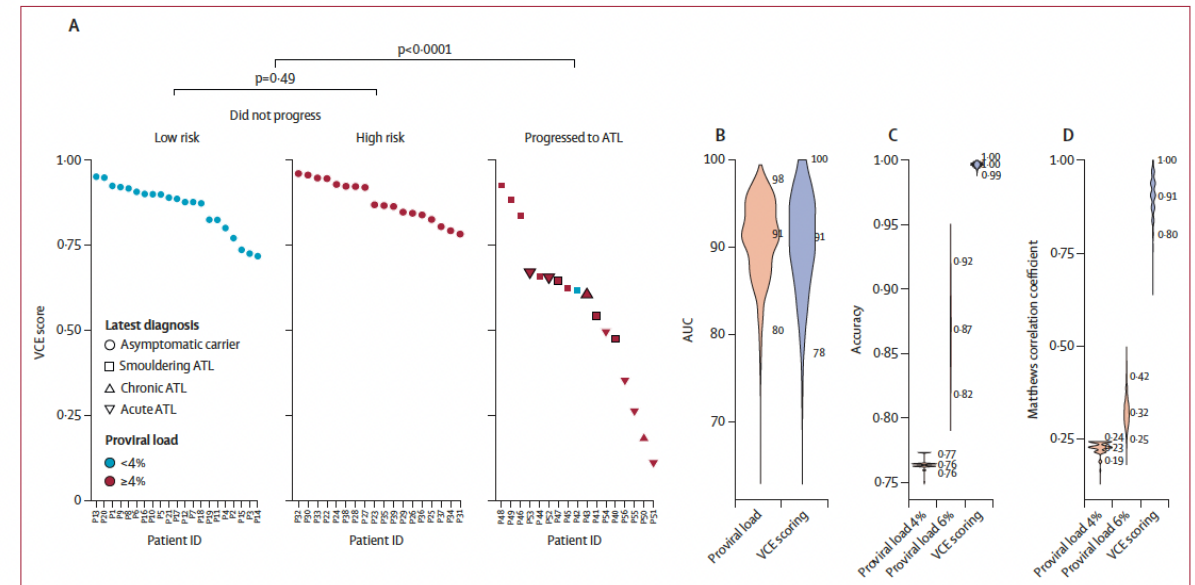
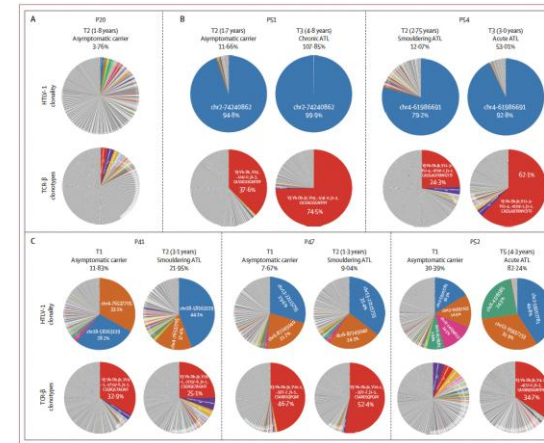


Figure 6: Performance of VCE scoring and proviral load in measuring HTLV-1 clonality and stratifying risk in asymptomatic carriers

Risk of ATLL development in HTLV-1 carrier

A viral clonality evenness score to predict progression to adult T-cell leukaemia in asymptomatic carriers of human T-lymphotropic virus type 1 in Japan: a retrospective longitudinal cohort study

Snehal Dilip Karpe, Maria Artesi, Jérôme Wayet, Keith Durkin, Vincent Hahaut, Kaoru Uchimaru, Junya Makiyama, Masako Iwanaga, Atee Utsunomiya, P Martijn Kolijn, Anton W Langerak, Arsène Burny, Ambroise Marçais, Olivier Hermine, Toshiki Watanabe, Michel Georges, Anne Van den Broeke

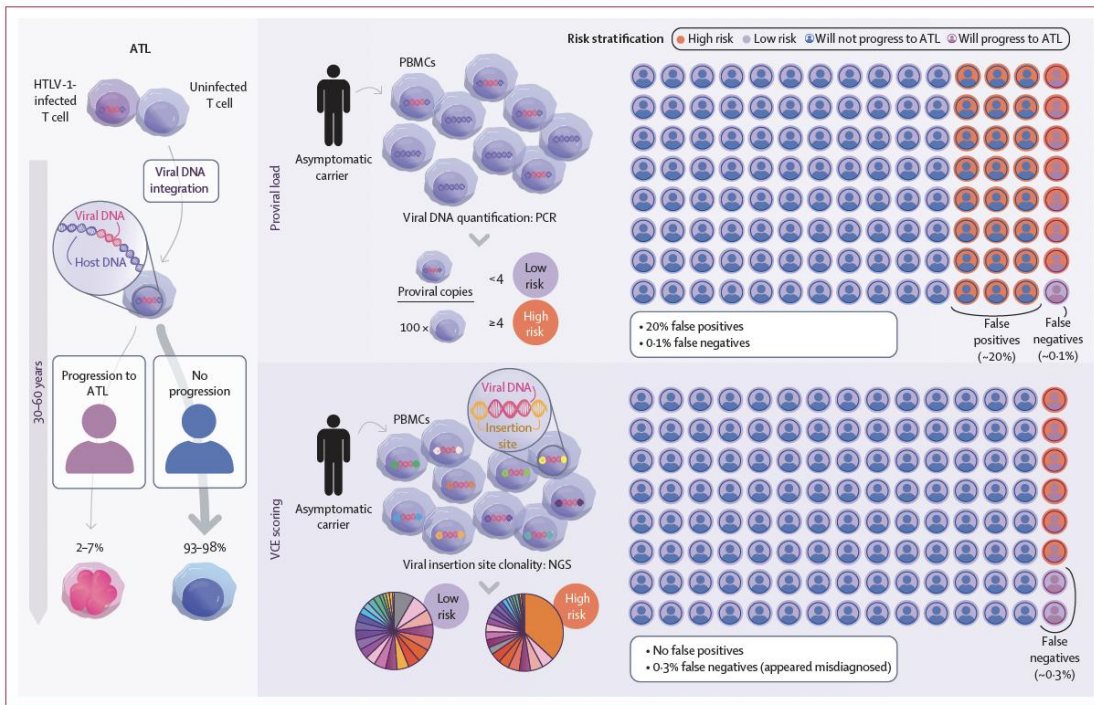


Figure 4: Risk stratification of asymptomatic HTLV-1 carriers on the basis of proviral load and VCE scoring
ATL=adult T-cell leukaemia/lymphoma. HTLV-1=human T-lymphotropic virus type 1. NGS=next-generation sequencing. PBMCs=peripheral blood mononuclear cells. VCE=viral clonality evenness.

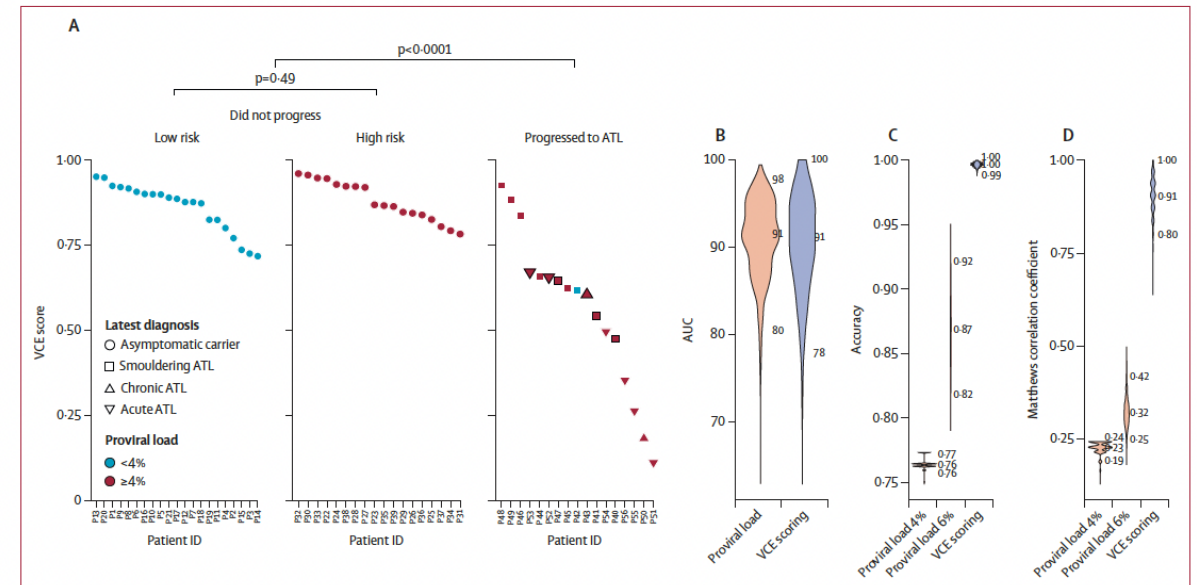
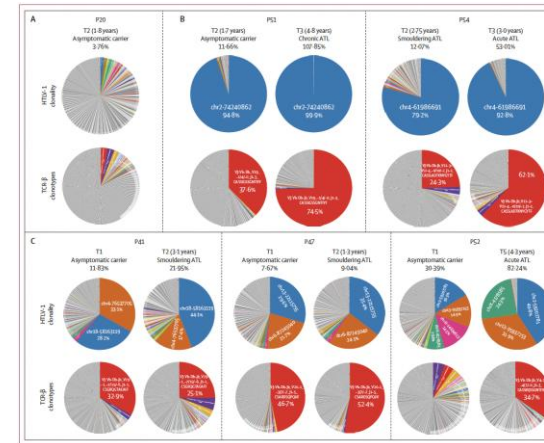


Figure 6: Performance of VCE scoring and proviral load in measuring HTLV-1 clonality and stratifying risk in asymptomatic carriers

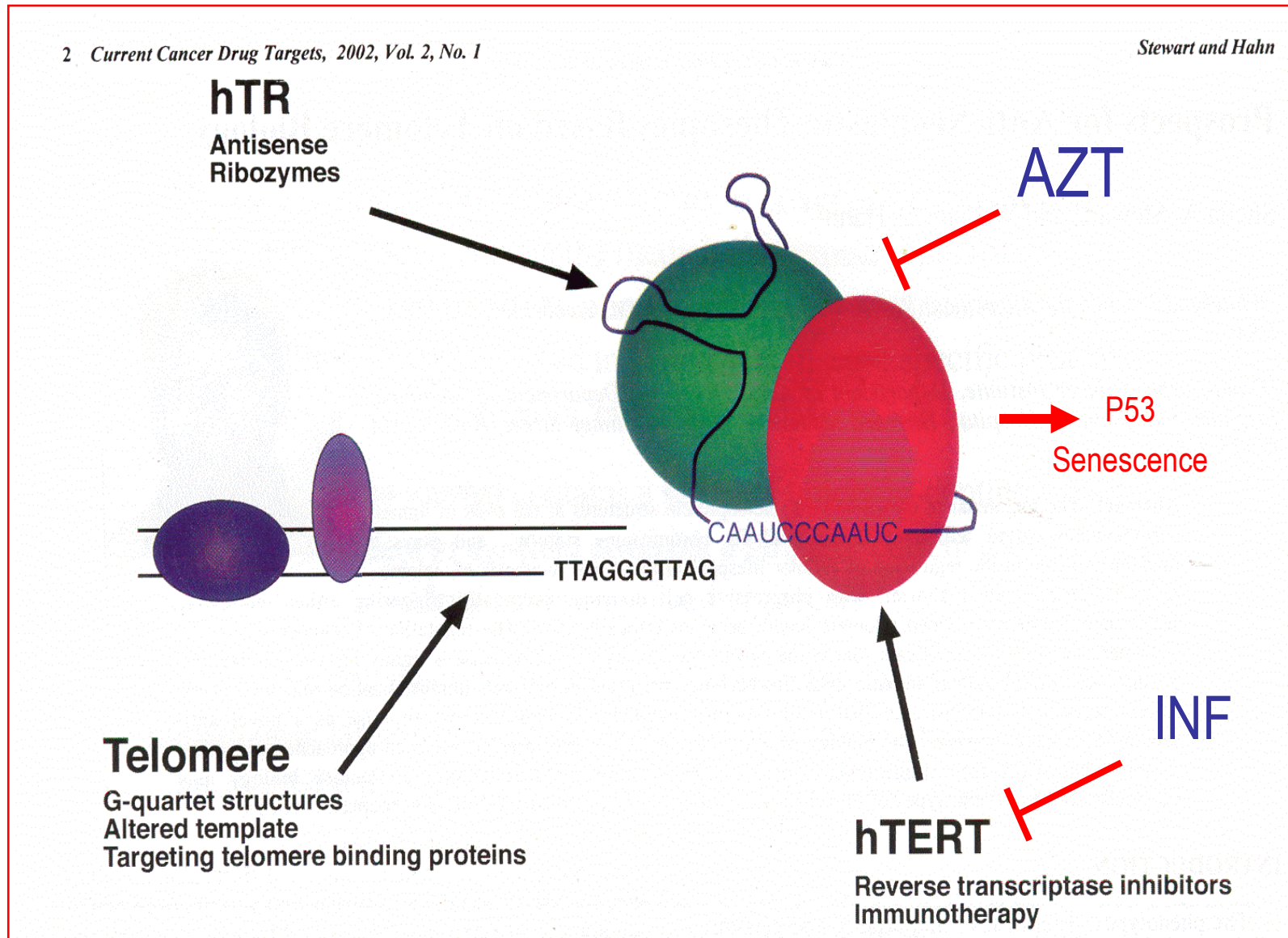
Ac Anti CCR4 (*L Cook and S Horwitz*)
Eradication of clones
(ADCC, Inhibition of Tregs)

Anti Viral therapy ?

Next-Generation Antiretrovirals: Dolutegravir and Tenofovir

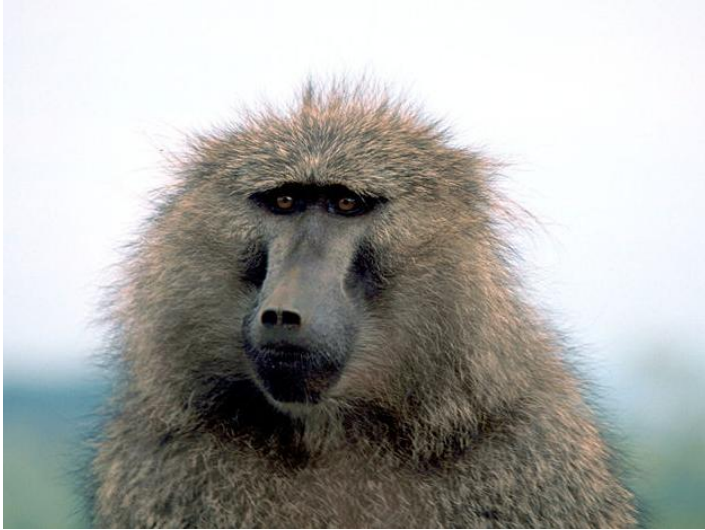
- Dolutegravir (DTG): HTLV-1 integrase strand-transfer inhibitor : prevents viral integration
- Tenofovir (TDF): nucleotide reverse transcriptase inhibitor : reduces viral replication
- Clinical evidence (HIV/HTLV-1 co-infected cohorts)(*Commun Med 2025 & CID 2026*):
 - . Significantly lower HTLV-1 PVL in patients on DTG-based ART vs non-DTG regimens
 - . Retrospective effect size >1 log PVL reduction in best-responding patients
- Preclinical: TDF + DTG significantly reduced HTLV-1c transmission in humanized mouse model (*Cell 2025*)
- Ongoing Phase IIb RCT: NCT07555431 (2026)
 - Design: DTG alone vs DTG + TDF in HTLV-1 mono-infected patients
 - Primary endpoint: change in PVL at 24 and 48 weeks
 - Strategic role: PVL reduction → ATL prevention; combination partner with MCL-1i

Targeting telomerase and telomeres Preferential senescence of infected cells



**Telomerase
inhibitor
*Imetelstat ?***

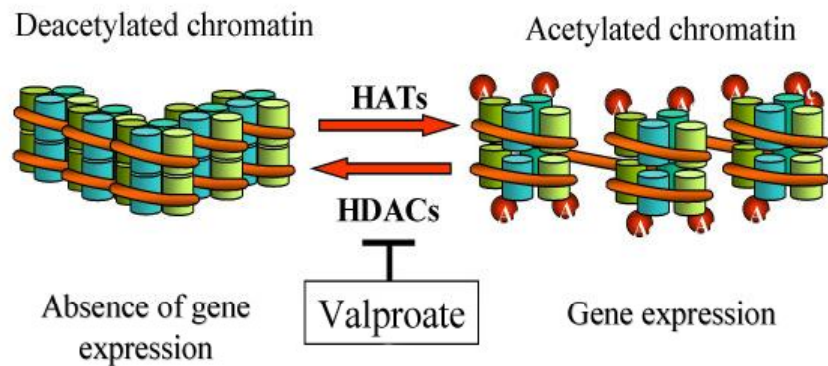
Monkey *Papio anubis*



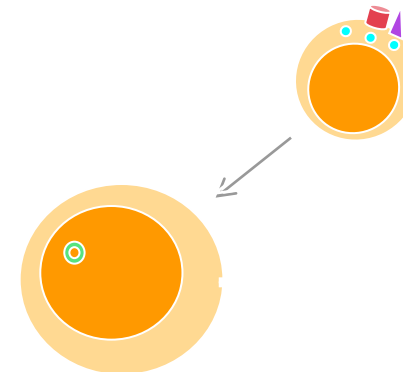
STLV-1 # HTLV-1

**Treatment by the combination of
AZT and Valproate sodium**

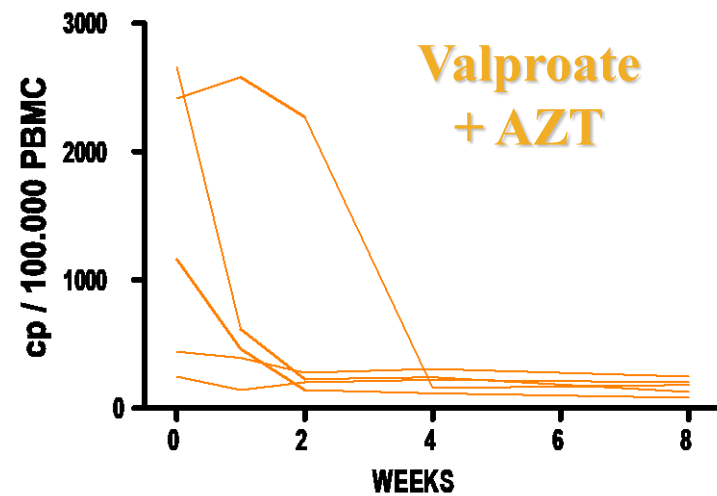
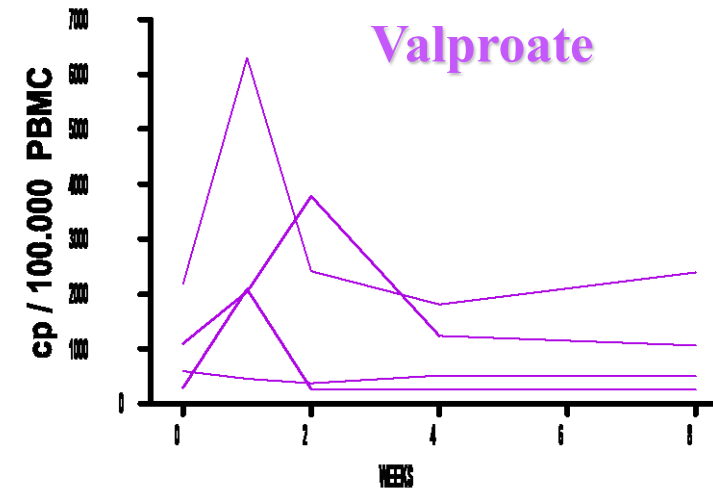
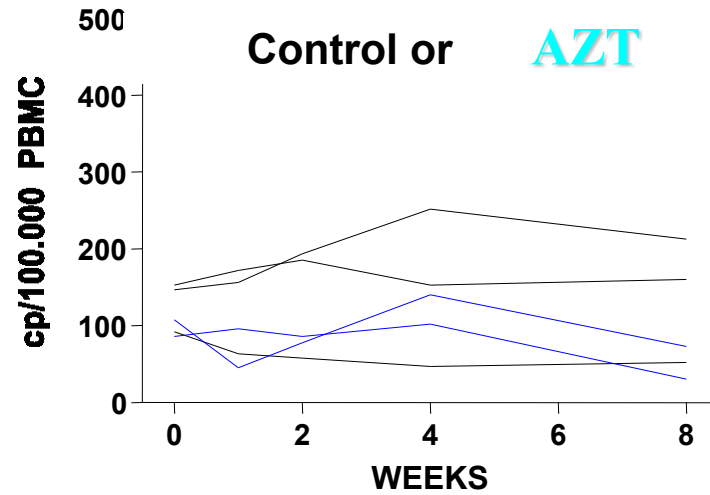
**Effect on viral load and
CD8 and CD4 number**



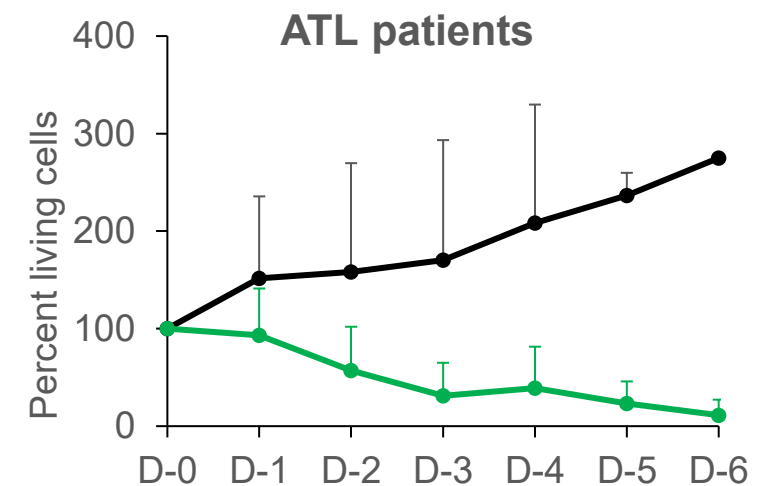
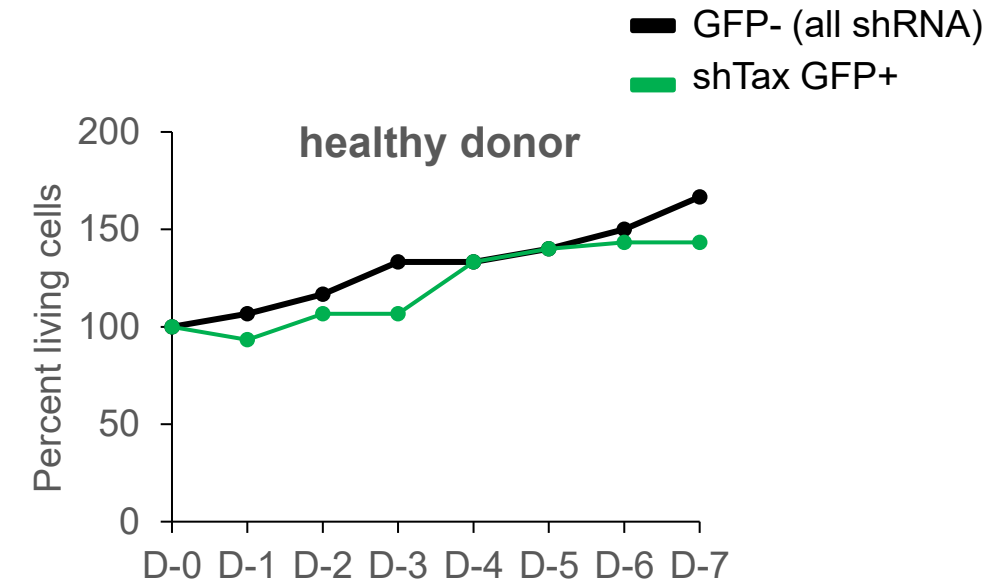
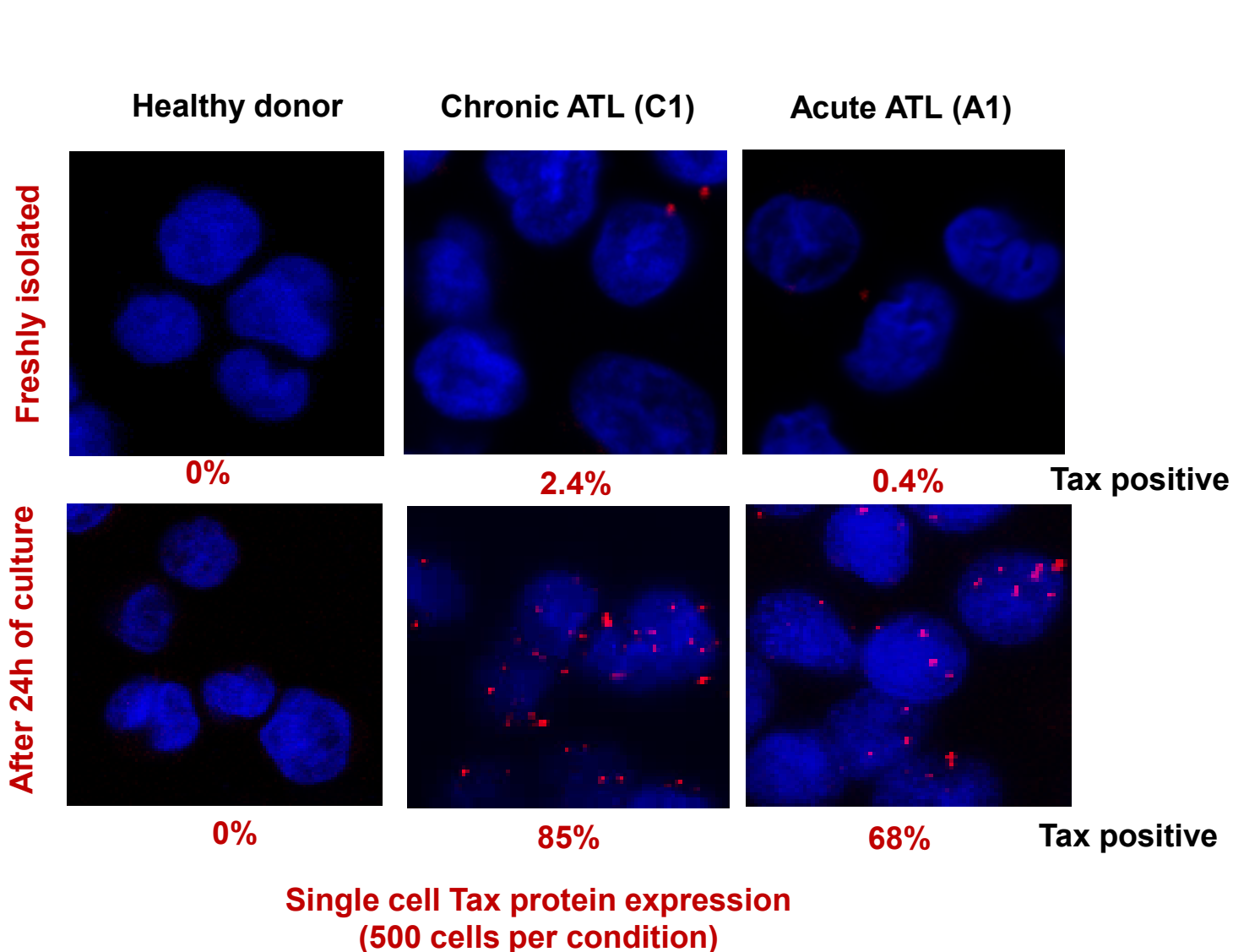
**Immune Response against
infected cells ? Senescence ?**



Effect of HDACi and AZT in Virus load

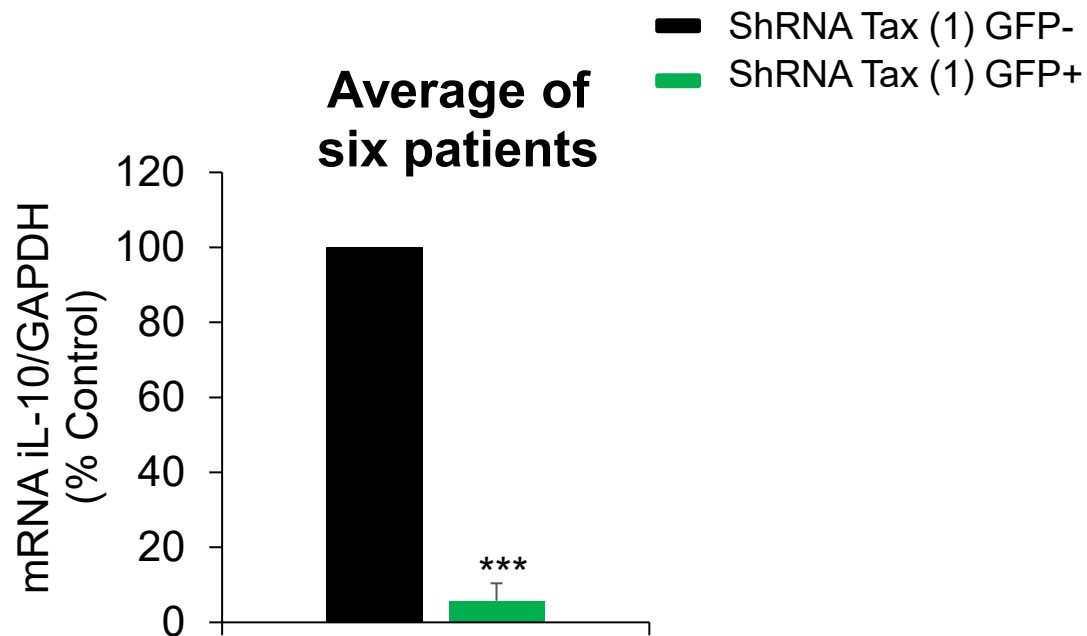


Primary cells from ATL patients express low levels of Tax and depend on Tax expression for their survival

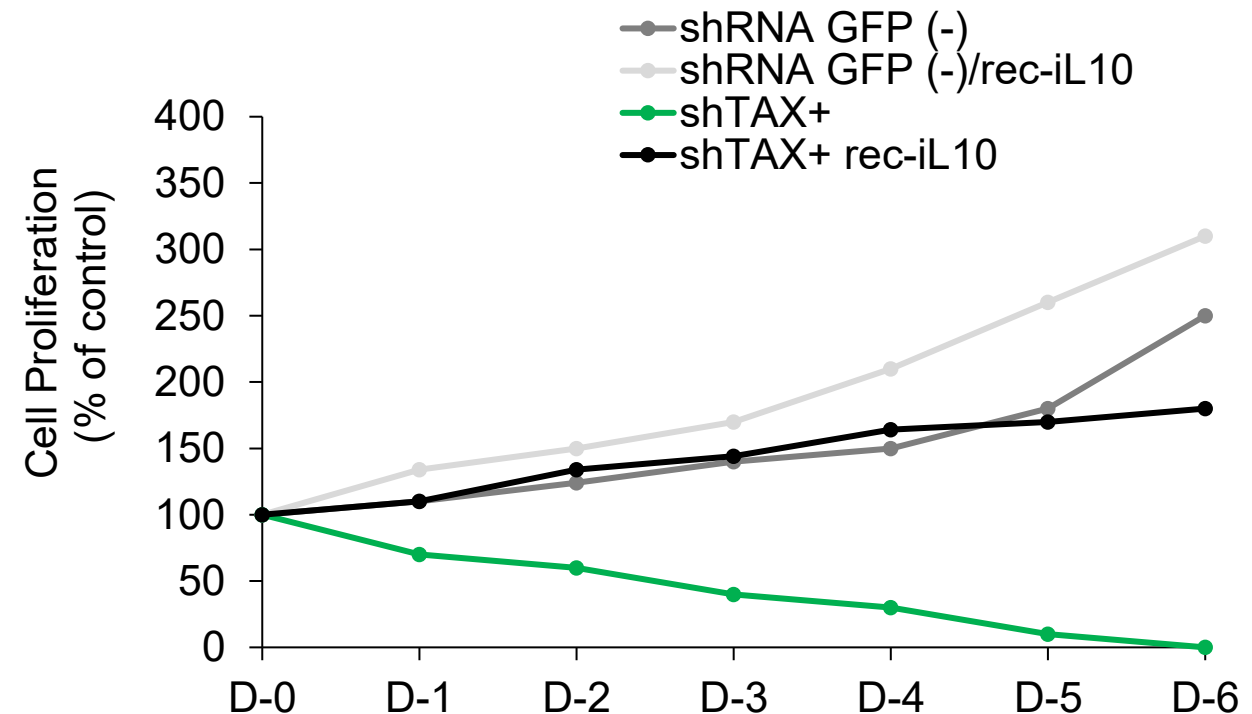


Critical role of Tax-induced IL-10 production in survival of primary ATL cells

IL-10 production by primary ATL cells depend on Tax expression



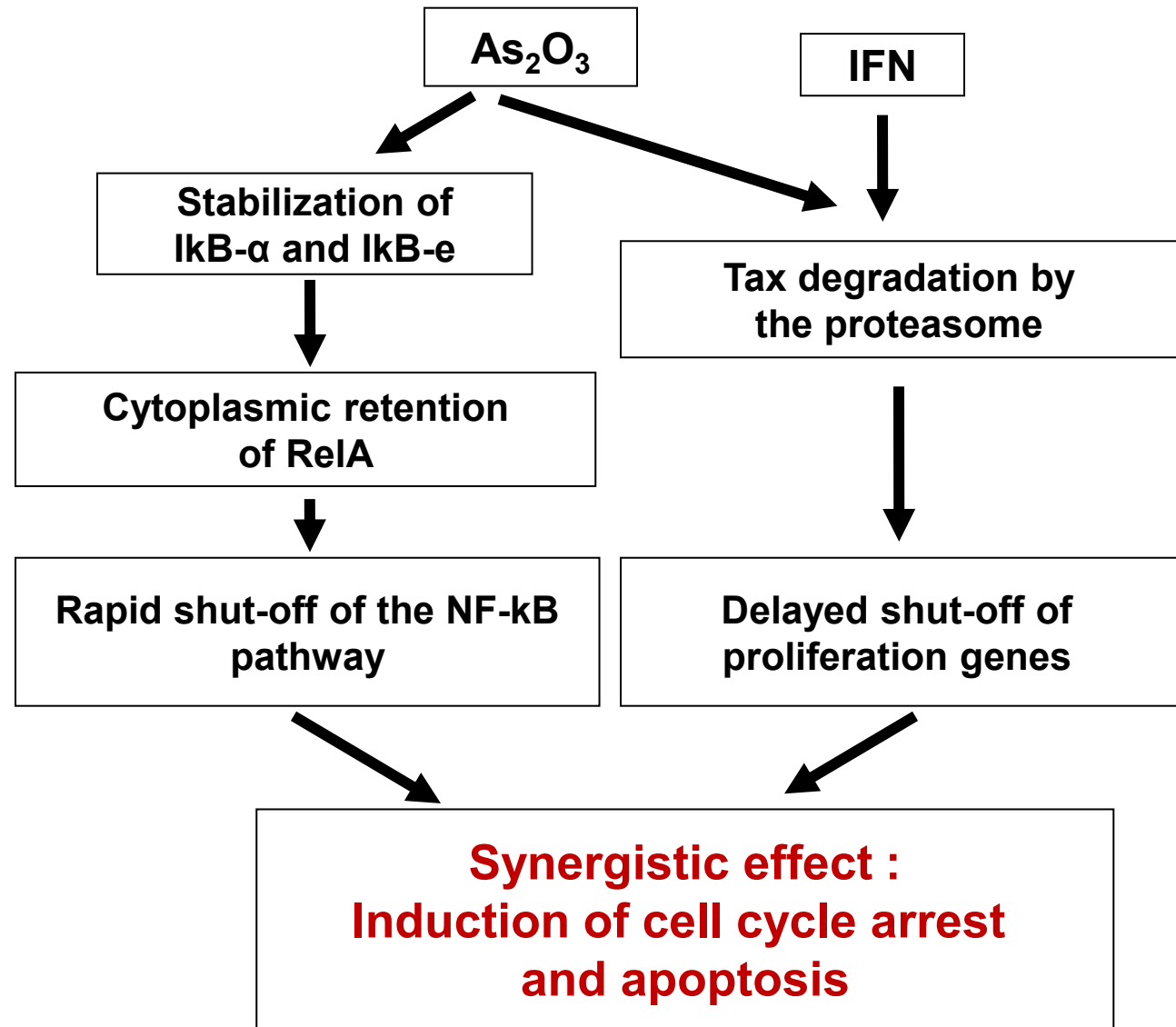
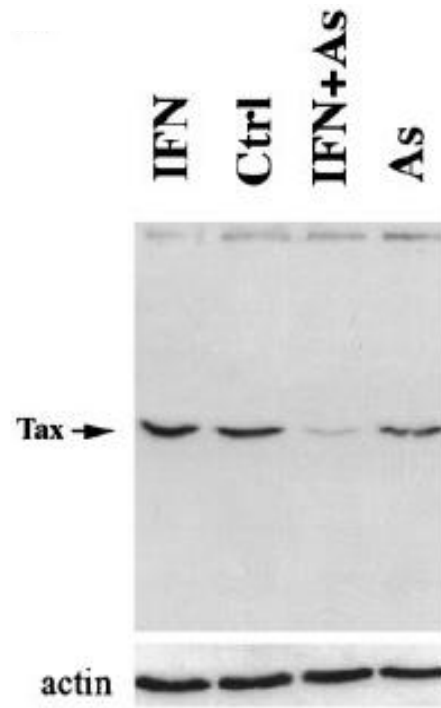
IL-10 can overcome the detrimental effects of Tax silencing on ATL cell survival



Ratio IL-6/IL-10 as a predictor of transformation ? (Bloch C,... Hermine O , Am J med in press)

Anti IL10 Antibodies as a treatment ? Or JAKi (but risk of immune suppression) like in RCD2 ?

Arsenic/IFN induces proteasomal Tax degradation



Arsenic/IFN cure murine ATL through abrogation of leukemia initiating cells (LIC) activity

Published December 6, 2010

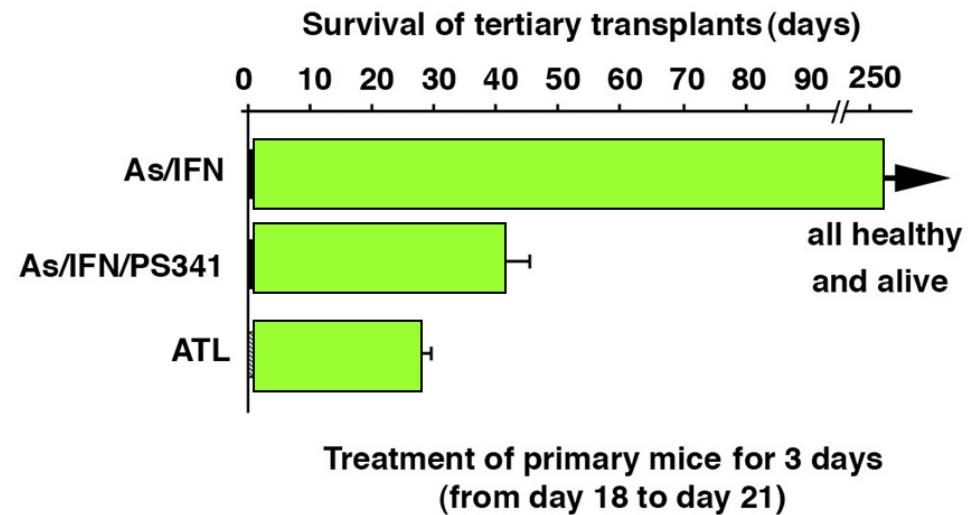
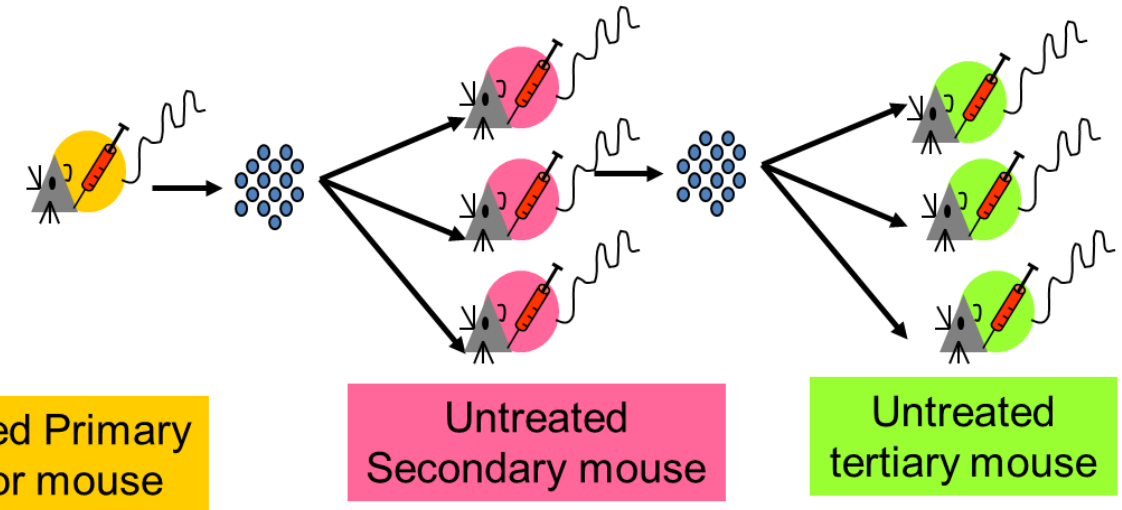
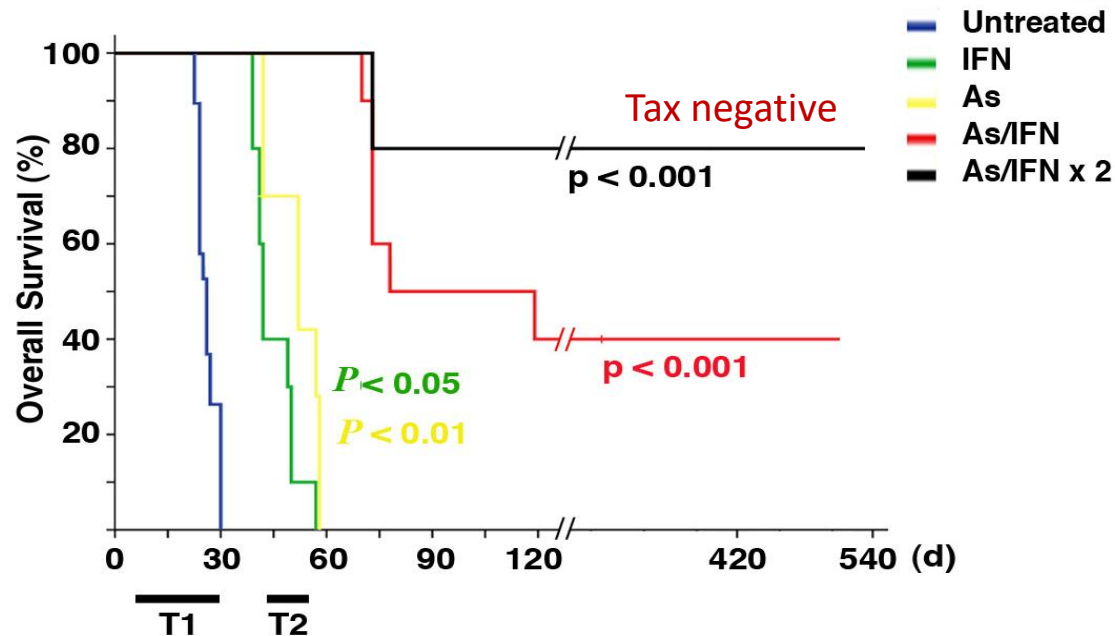
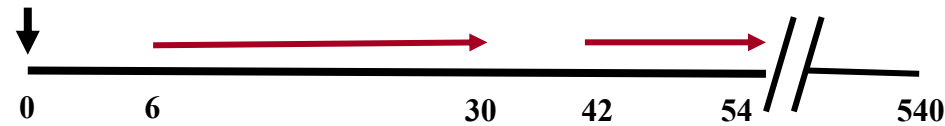
JEM

Brief Definitive Report

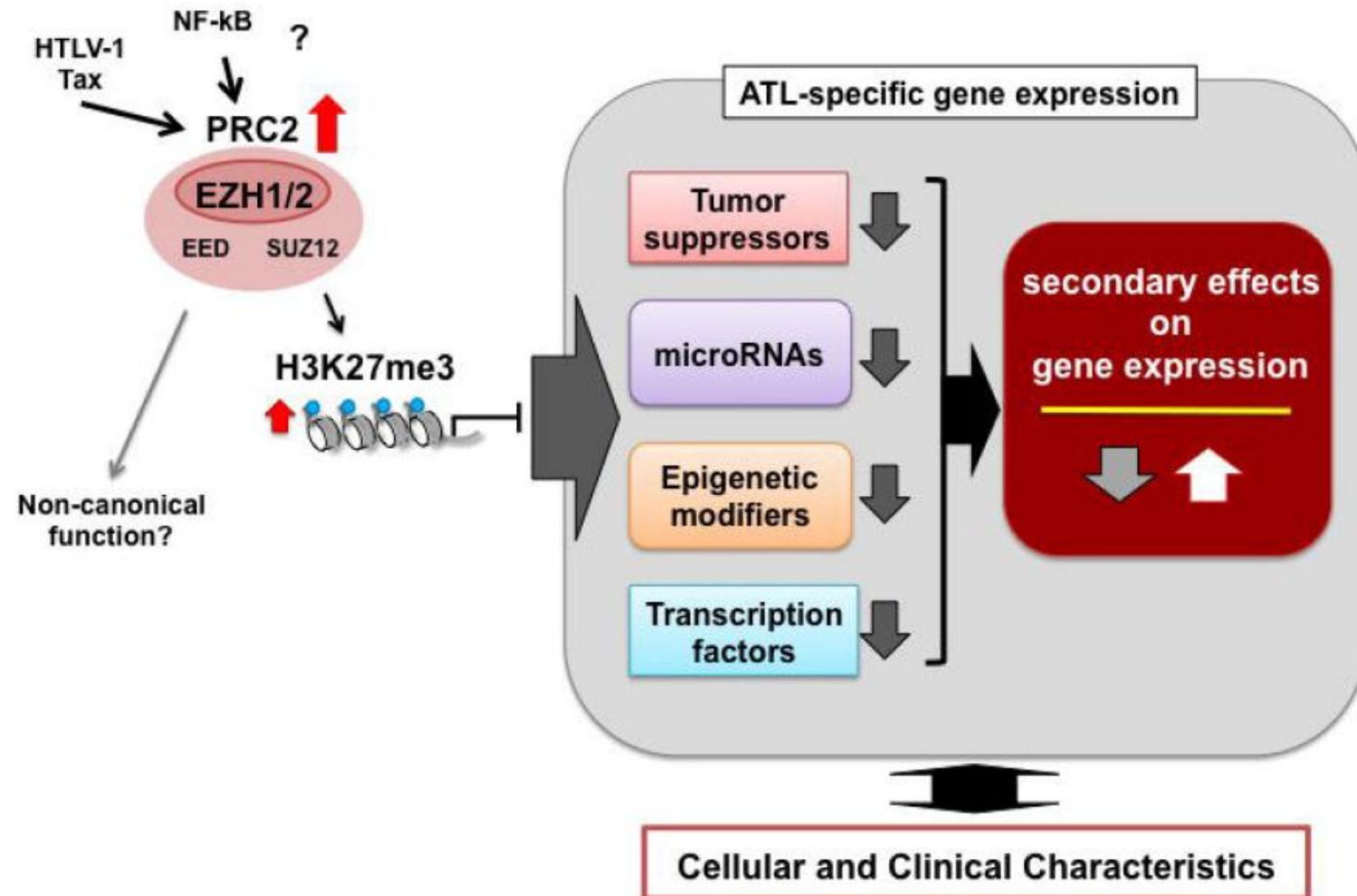
Therapy-induced selective loss of leukemia-initiating activity in murine adult T cell leukemia

Hiba El Hajj,¹ Marwan El-Sabban,² Hideki Hasegawa,^{4,5} Ghazi Zaatari,³ Julien Ablain,⁶ Shahrzad T. Saab,³ Anne Janin,⁷ Rami Mahfouz,³ Rihab Nasr,¹ Youmna Kfoury,¹ Christophe Nicot,^{8,9,10} Olivier Hermine,¹¹ William Hall,⁵ Hugues de Thé,⁶ and Ali Bazarbachi¹

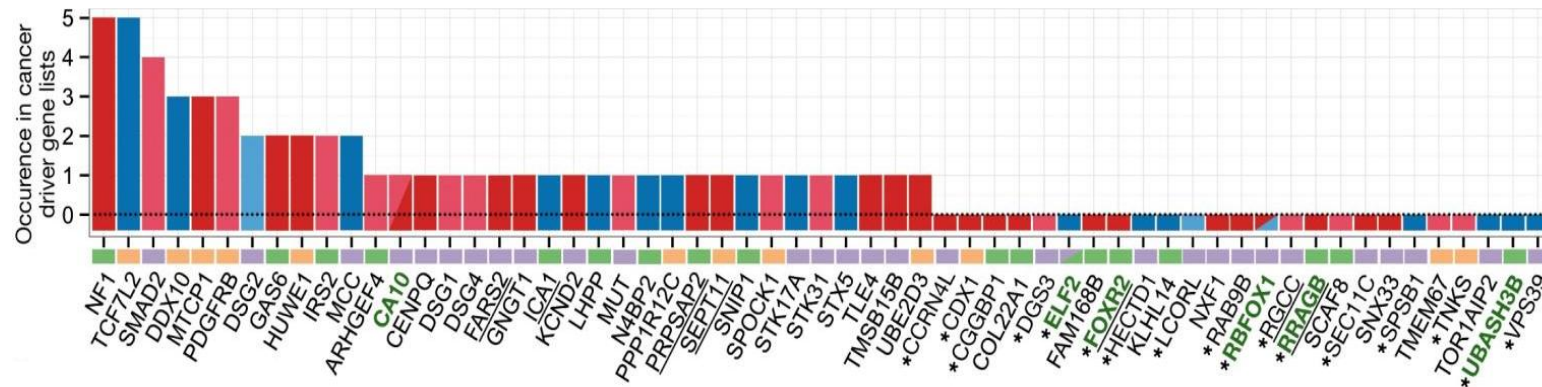
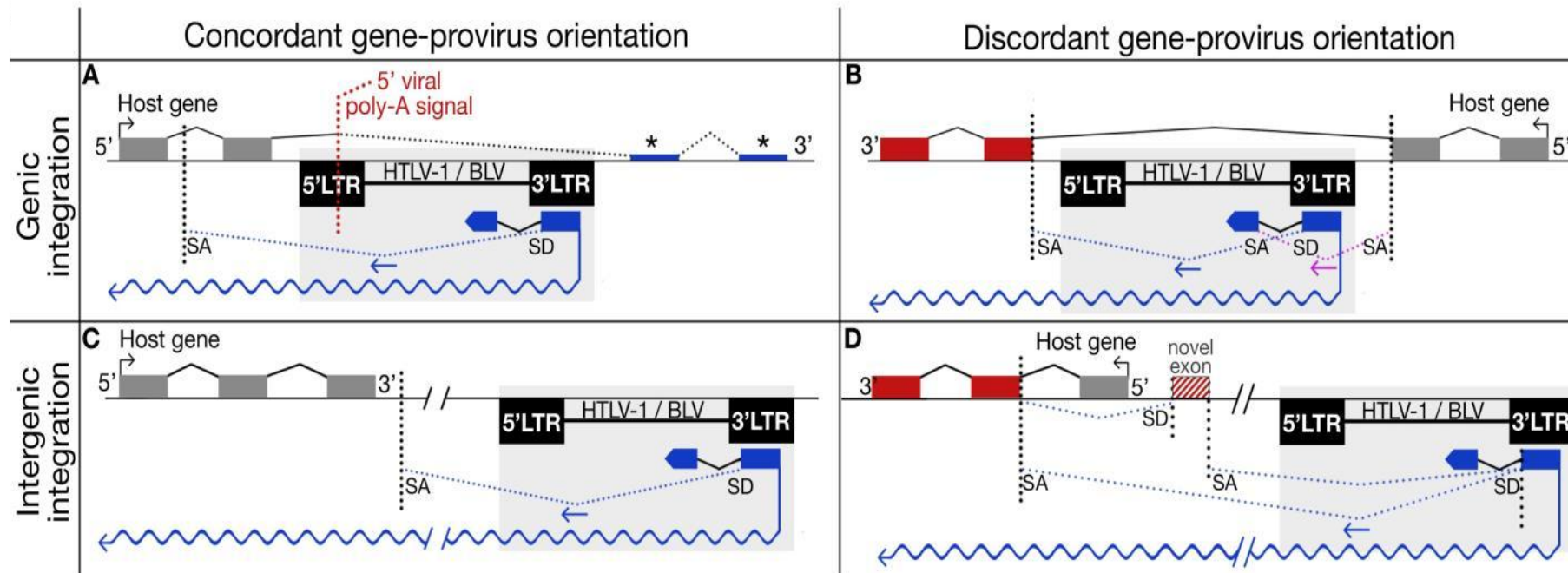
ATL Cells



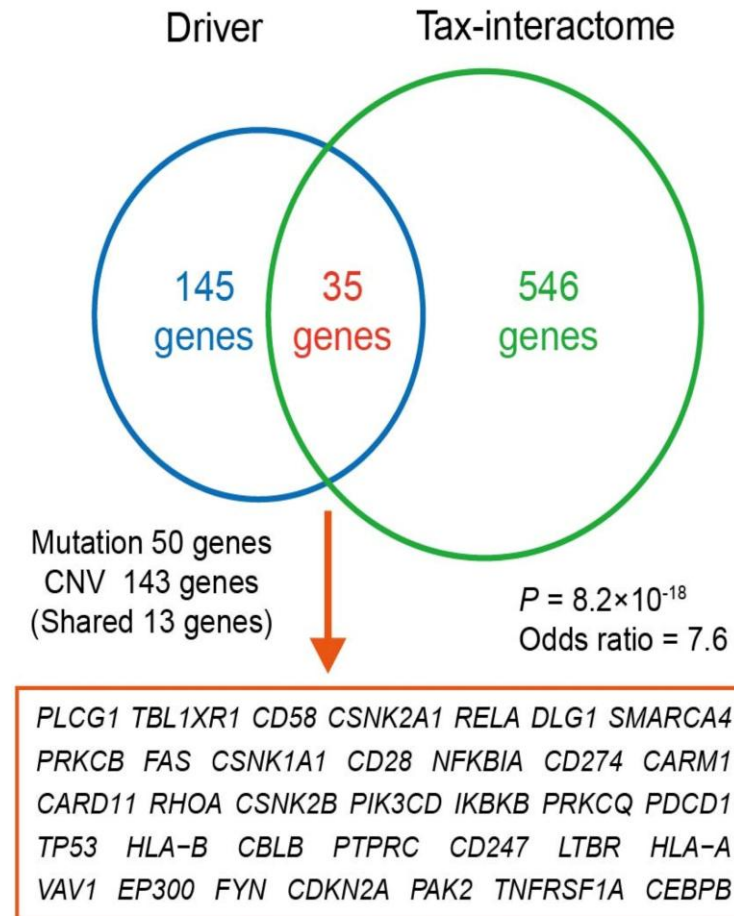
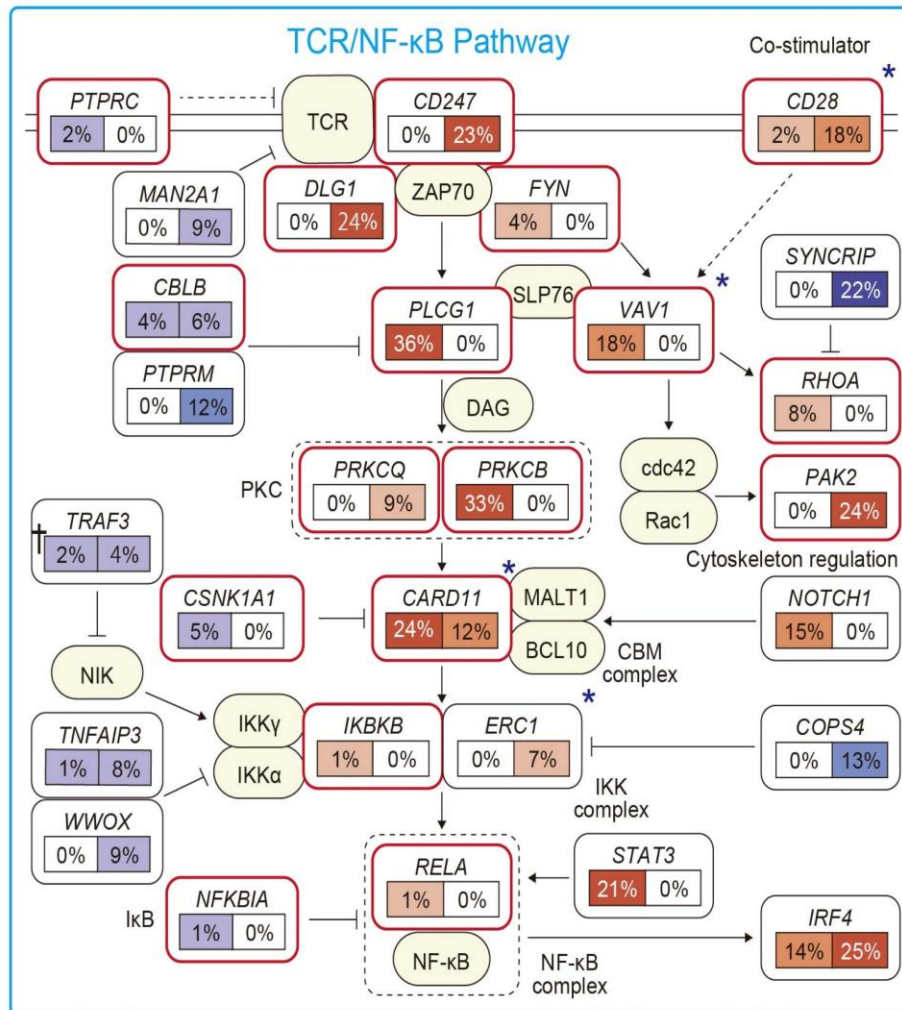
Epigenetic and ATLL : EZH2i a universal target



Genetic signature : Clonal signature that might be a target ?



Mutations Landscape in ATLL



Treatment of ATLL

ATL: clinical aspects and Shimoyama classification

- Aggressive proliferation of mature, activated **CD4+CD25+CD7-CD3+/- T-** cells with clonal integration of the provirus
- Adult age** (median 56y.)
- Long latency period** (20 to 40 y.)
- Important tumoral syndrome:**
 - Lymphadenopathies
 - Hepatosplenomegaly
 - Visceral lesions (lung, skin, GI, CNS...)
- Paraneoplastic hypercalcemia**
- Opportunistic infections**

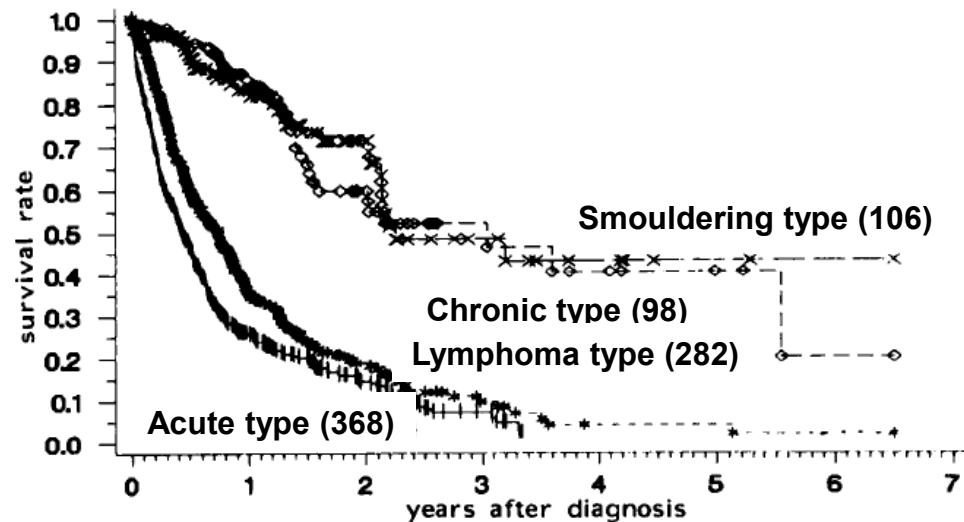
		Indolent ATL		Aggressive ATL	
	Healthy carrier	Smoldering ATL	Chronic ATL	Acute ATL	ATL lymphoma
HTLV-I Serology	+	+	+	+	+
Clonal integration of provirus	- (blood)	+ (blood)	+ (blood)	+ (blood)	+ (lymph nodes)
Lymphocyte count	Normal	Normal	Elevated	Elevated	Normal
Abnormal cells (%)	< 5%	> 5%	> 5%	> 5%	< 1%
Hypercalcemia	-	-	-	+	+
LDH levels	Normal	< 1.5 N	< 2N	> 2N	> 2N
Skin or lung involvement	-	-	+	+	+
Bone, GI or CNS involvement	-	-	-	+	+

HTLV1 related lymphoproliferation : Universal Treatment ?

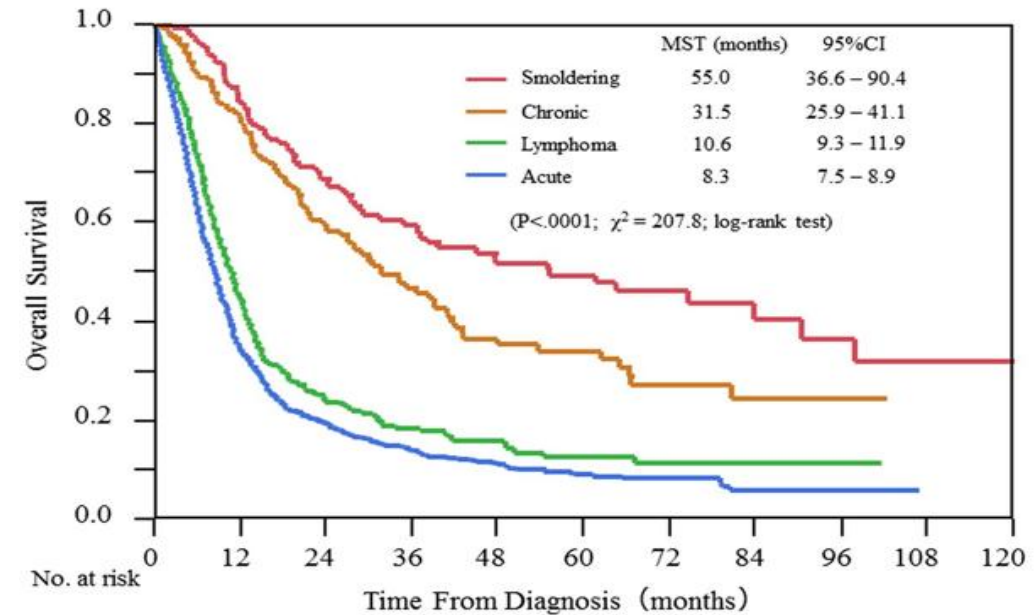
- Immunocompromised patients
- Virus replication vs disturbance of immune homeostasis
- Heterogeneity of the disease (somatic mutations ?, Integration site ?, immune system ?)
- Intra clonal variation
- Targeting Tumoral cells vs Targeting the virus
- Targeting Microenvironnement (*In vivo* vs *In vitro*)
- Immune therapy against tumoral cells
- Personalized treatment : **Achille heel ?**

ATL has a dismal prognosis

Overall survival of ATL in Japan



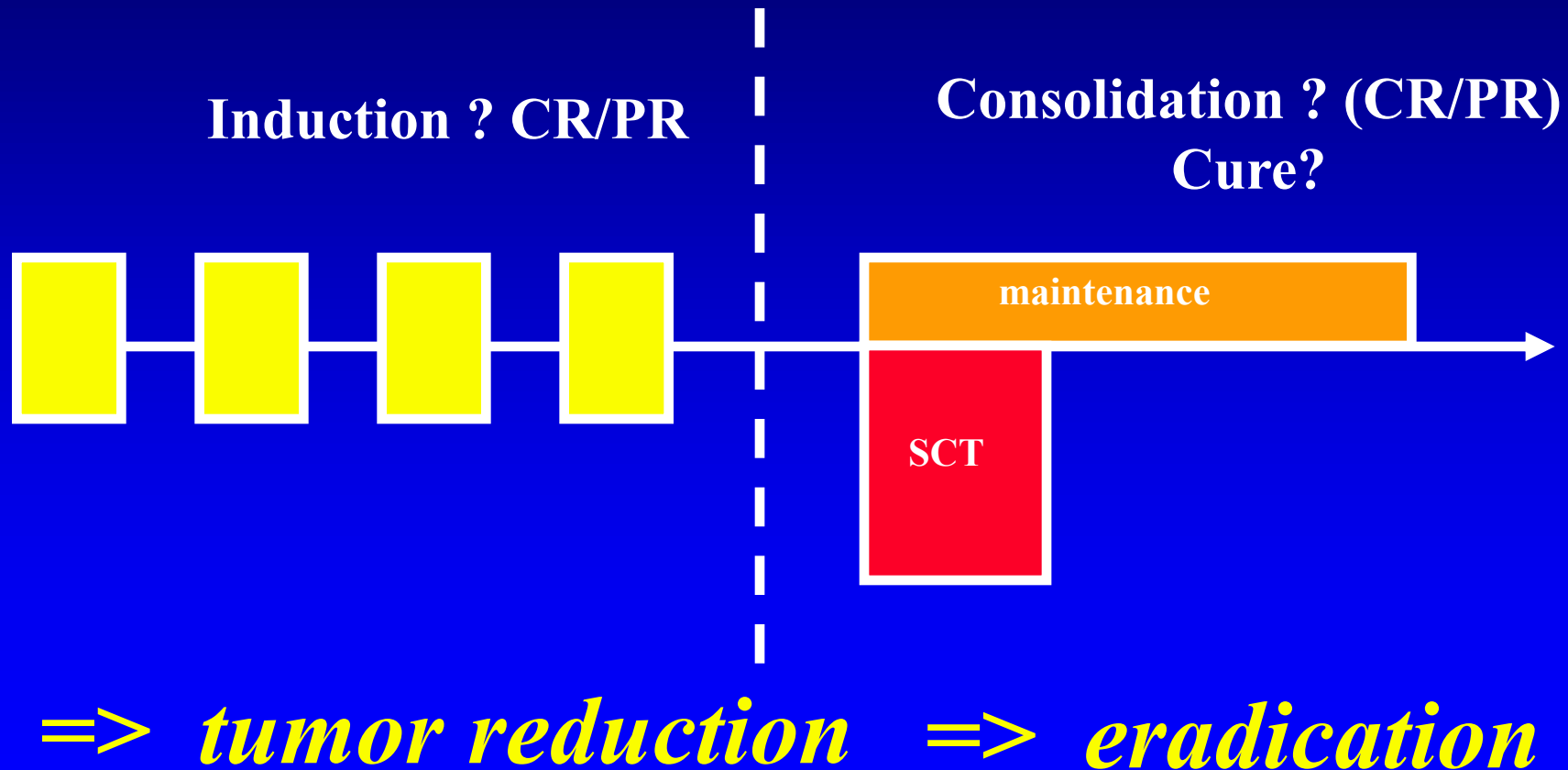
Shimoyama et al., 1992



Katsuya H, et al. Blood 2015

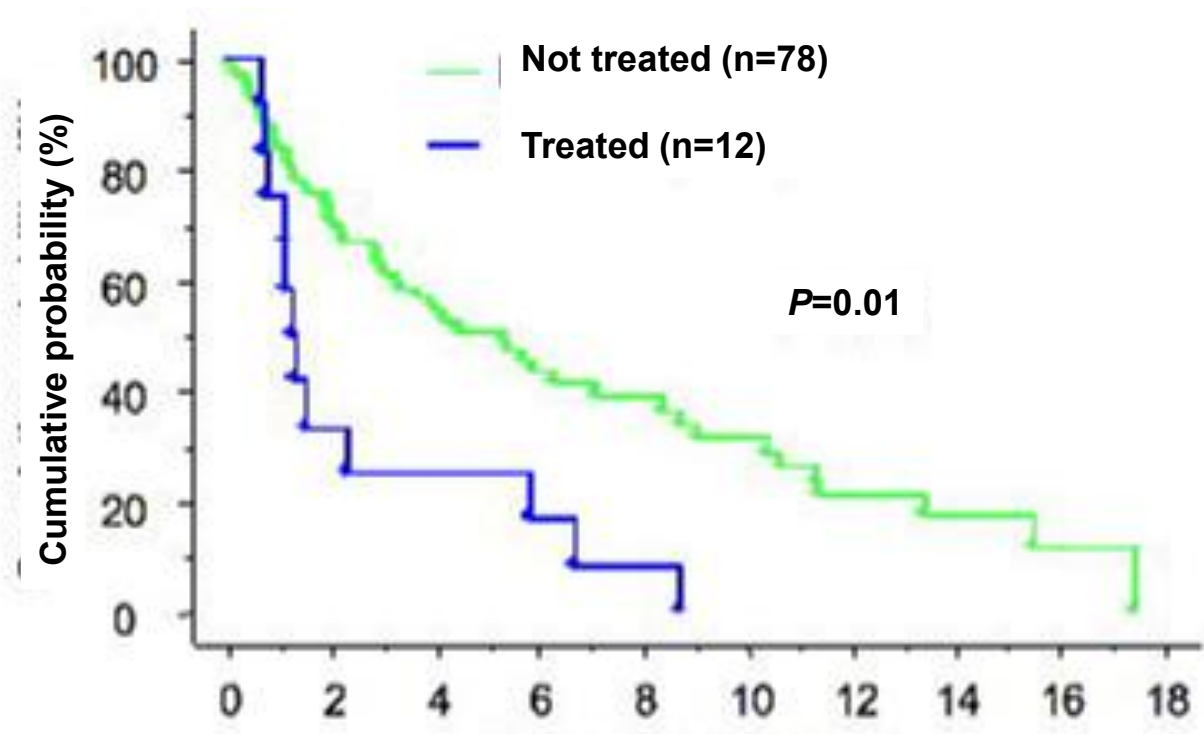
After 3 decades, OS has not improved!

Optimal treatment of ATL



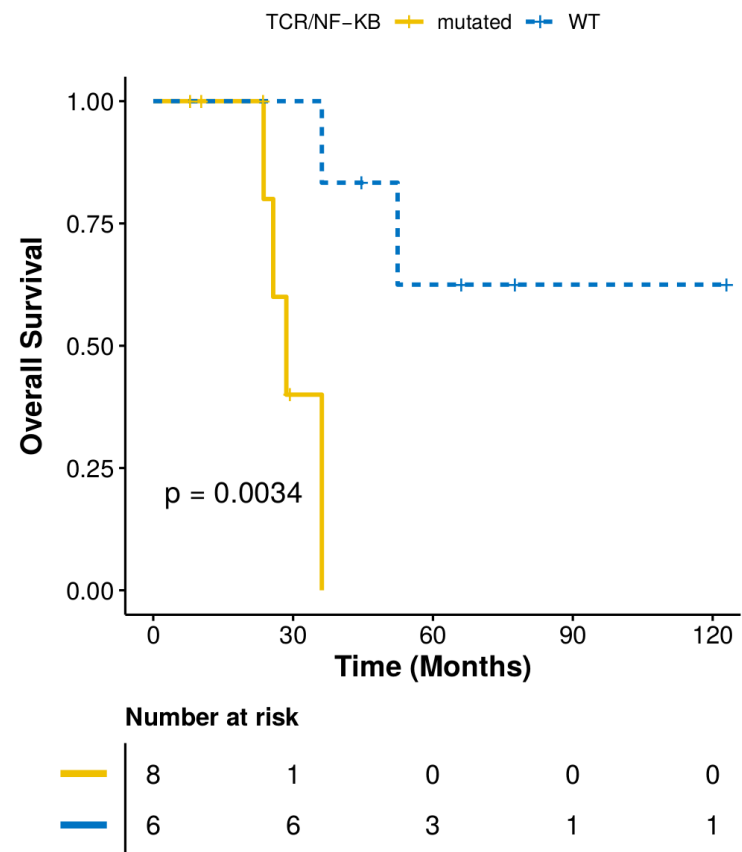
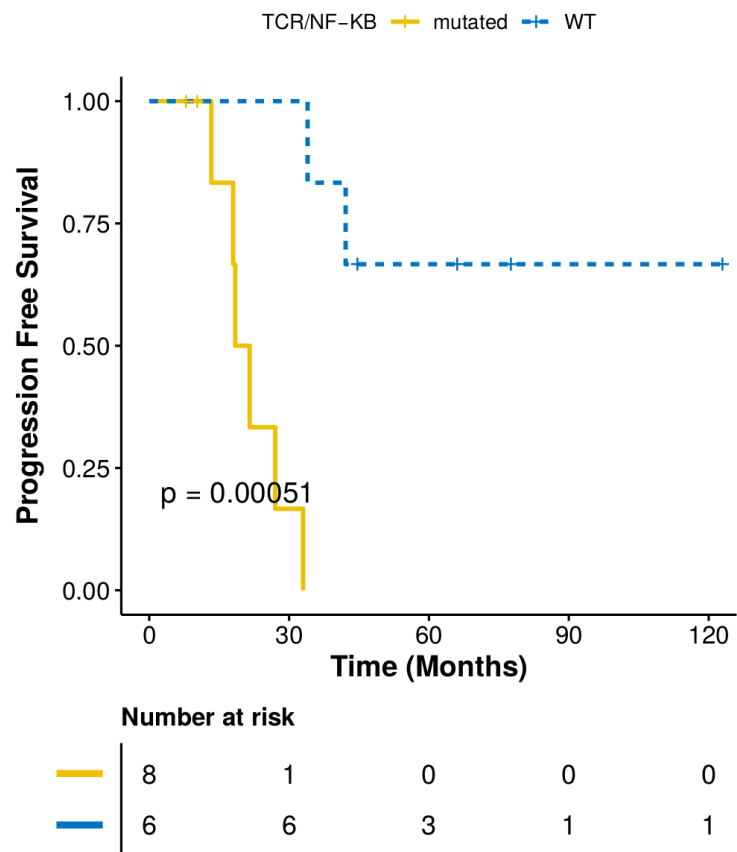
Watch and wait in indolent ATL

Smoldering/chronic ATL



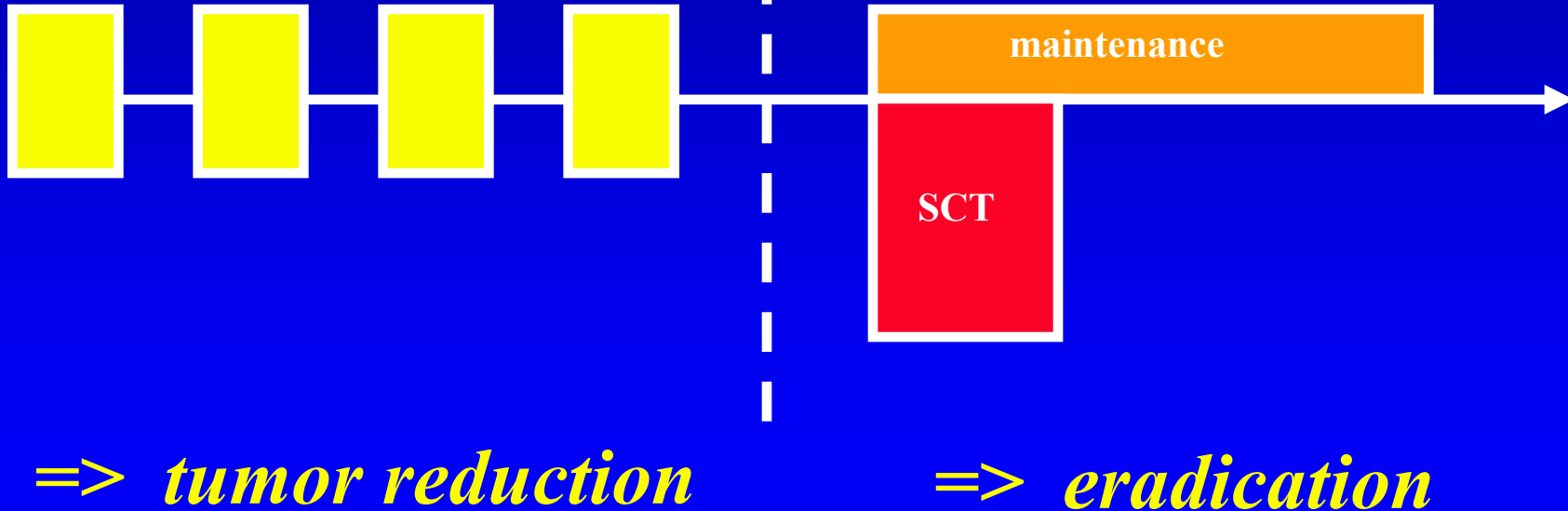
Molecular Studies

Prognosis of Chronic Forms

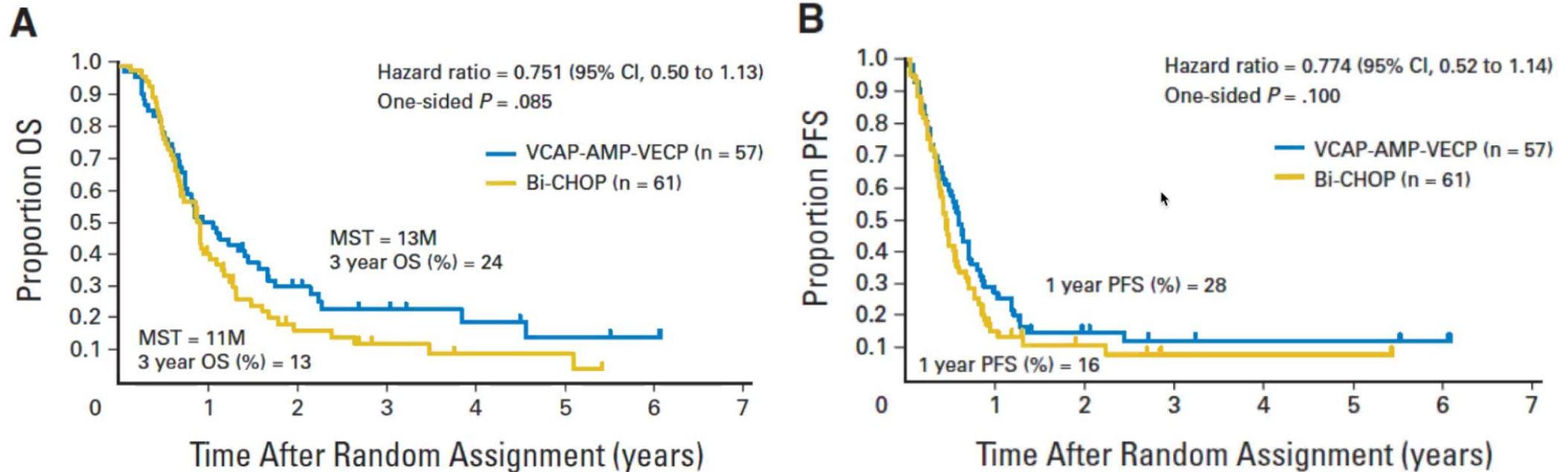


Optimal treatment of ATL

Chemotherapy



Chemotherapy for ATL



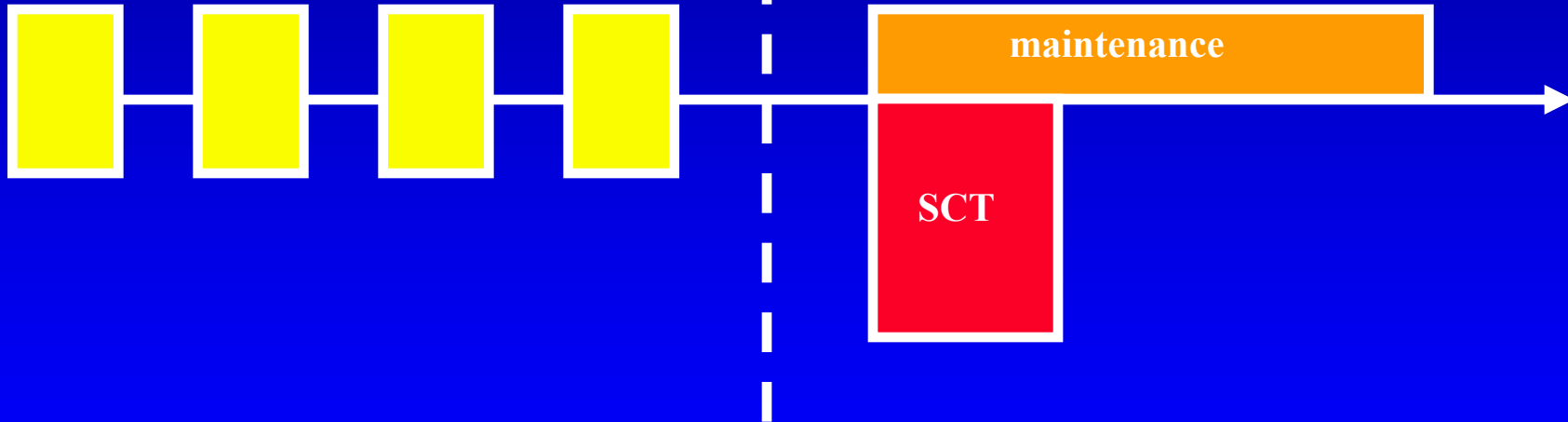
3 year OS: 24% vs 13% (ns)

PFS: 28% vs 16% (ns)

Tsukasaki et al. J Clin Oncol 2007

Optimal treatment of ATL

**Chemotherapy
+ Antibodies**



=> tumor reduction

=> eradication

Monoclonal Antibodies

Anti CD25 Antibodies: moderate activity, indolent ATL

Alemtuzumab (CAMPATH-1H; anti-CD52 antibody): few patients, transient response, mostly in Blood. High rate of infections when combined with chemotherapy

SGN-35 (brentuximab Vedotin; anti CD30): CD30 is expressed in a subgroup of patients

Anti CC chemokine receptor 4 (KW-0761): ATL cells express CCR4, Treg express CCR4, ADCC increase

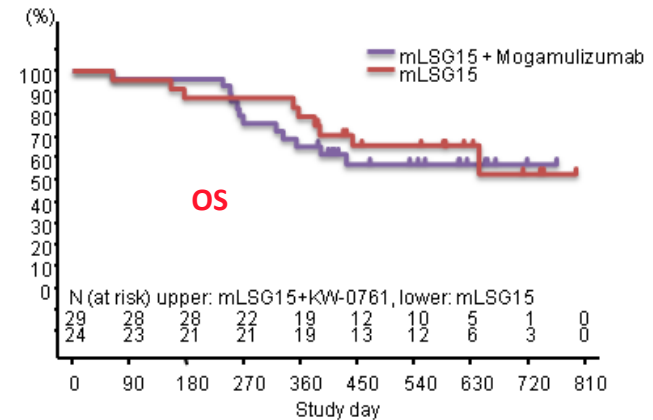
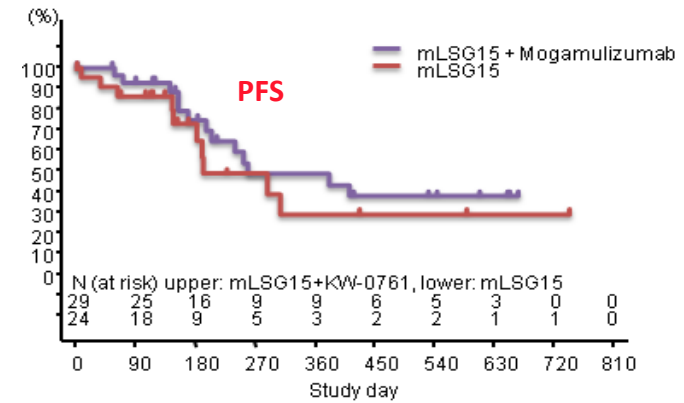
Anti KIR (KIR3DL2)

Anti transferrin receptor Antibodies (A24): promising preclinical studies

Randomized trial: Chemotherapy (LSG15) +/- Mogamulizumab in CCR4+ newly diagnosed ATL (acute, lymphoma or unfavorable chronic)

Response by disease site

Group	Site	N	CR%	ORR (%)
mLSG15 +Mogamulizumab	Lymph nodes/lesions	26	92	92
	Cutaneous	8	50	75
	Blood	14	100	100
mLSG15	Lymph nodes/lesions	22	73	77
	Cutaneous	5	60	80
	Blood	7	43	100



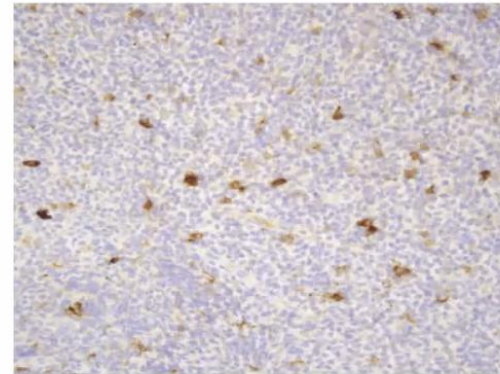
Brentuximab in ATLL (Necker)

CD30 expression in ATL

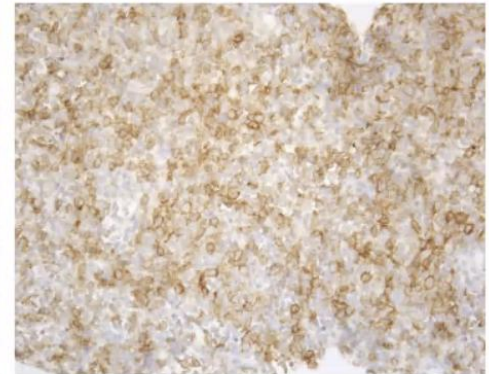
ATL	N=70	%
Forme Lymphoma	43	6%
Forme Acute	17	25%
Forme chronic	3	4%
Unknown	7	10

Score according to C. Bossard	N=70	%
Score 0 (<5%)	20	29%
Score 1 (5-24%)	12	17%
Score 2 (25-49%)	8	11%
Score 3 (50-75%)	16	23%
Score 4 (>75%)	14	20%

(Bossard *et al*, Blood 2014)



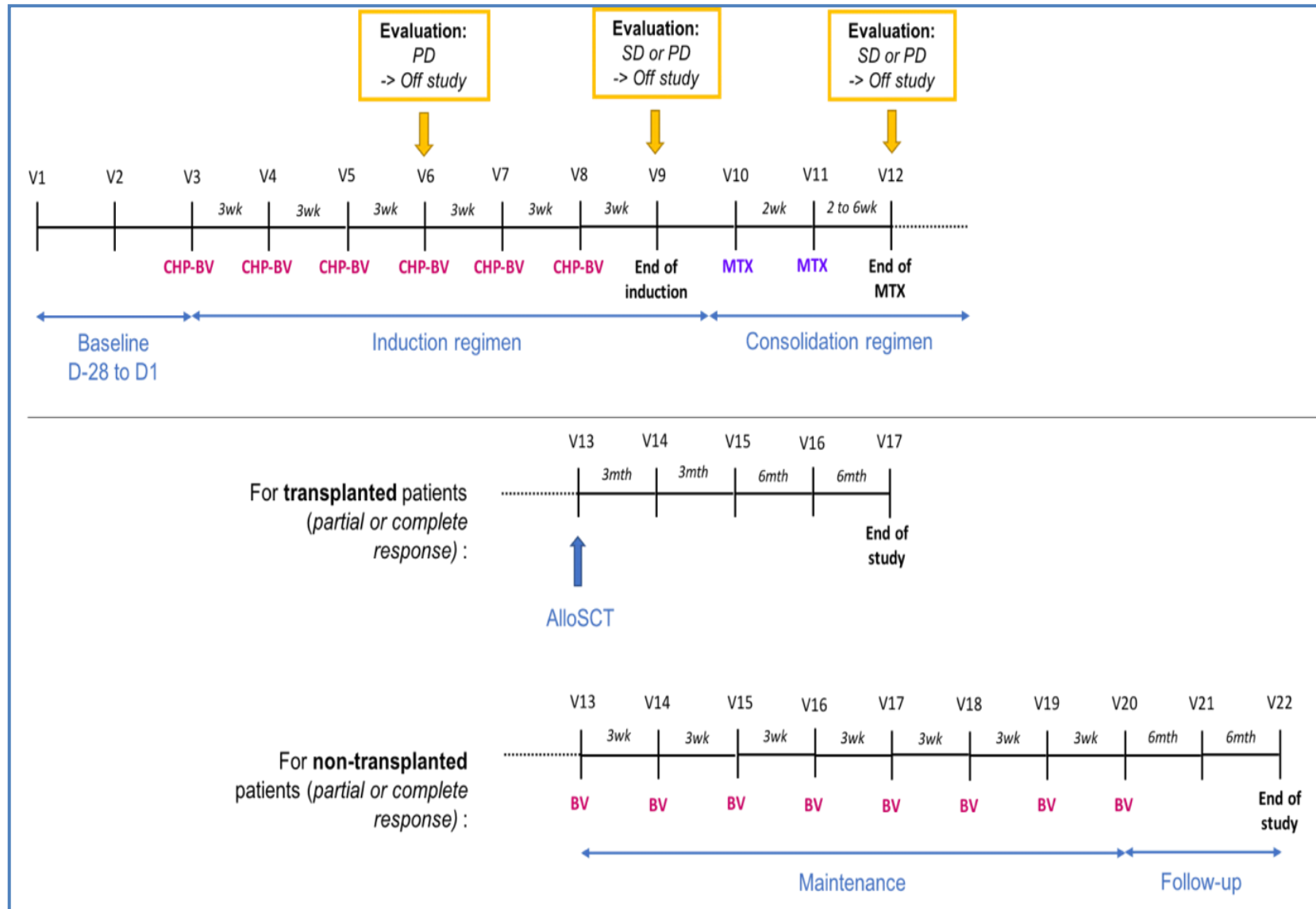
Score 1



Score 3

Naveau L. et al. *In preparation*

Study of BV in ATLL



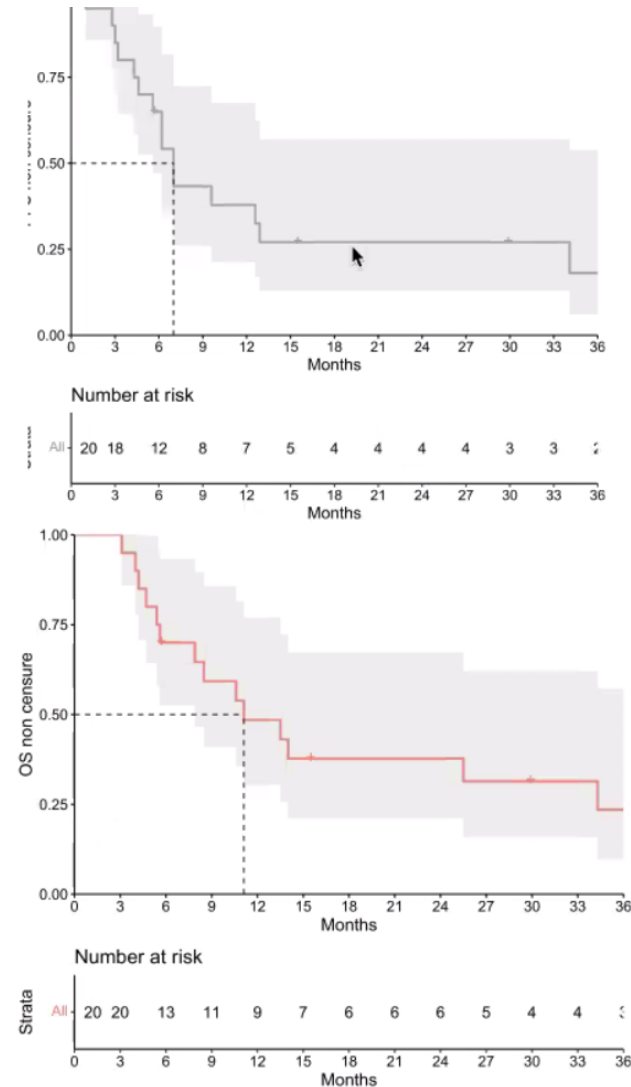
Brentuximab in ATLL (Necker)

	n =20 (%)
Age (median)	46 yeays (range 28-65)
Acute	13 (65)
Lymphoma	7 (35)
CNS involvement	
Yes	9 (45)
No	11 (55)
JCOG-PI (PS or hypercalcemia)	
High	10 (50)
Low	10 (50)

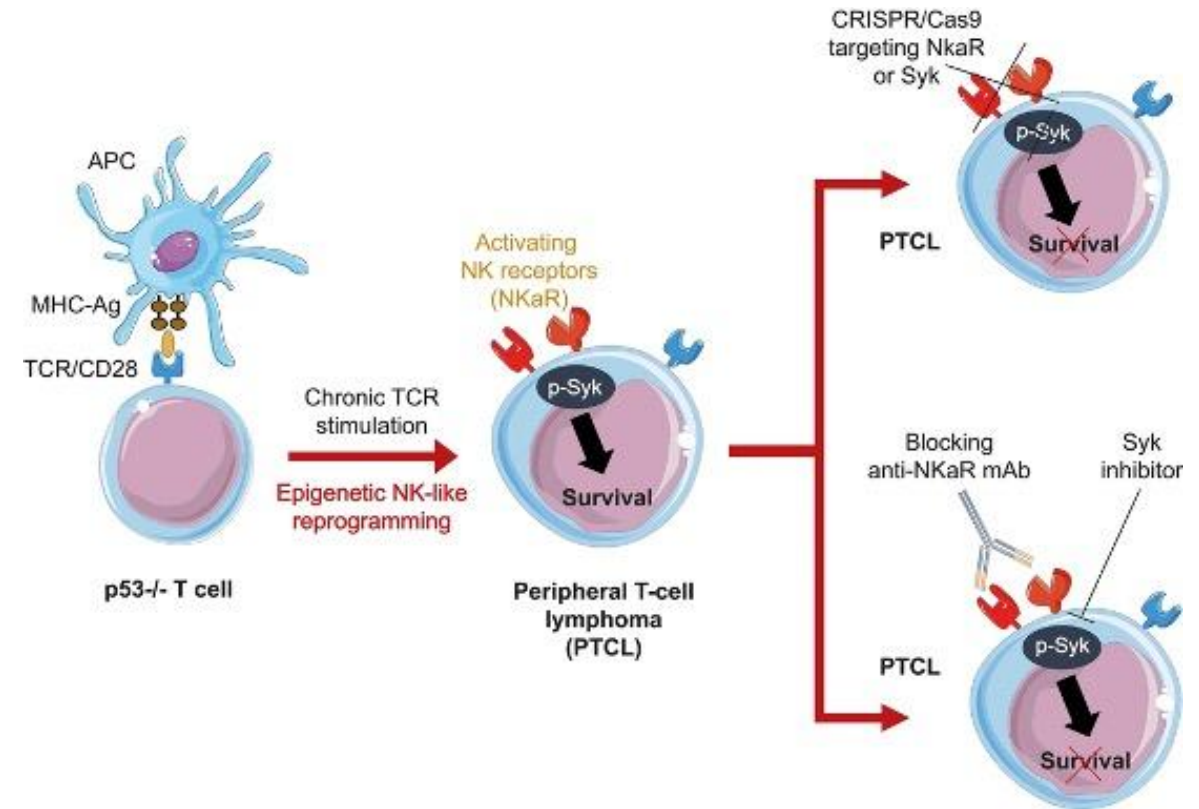
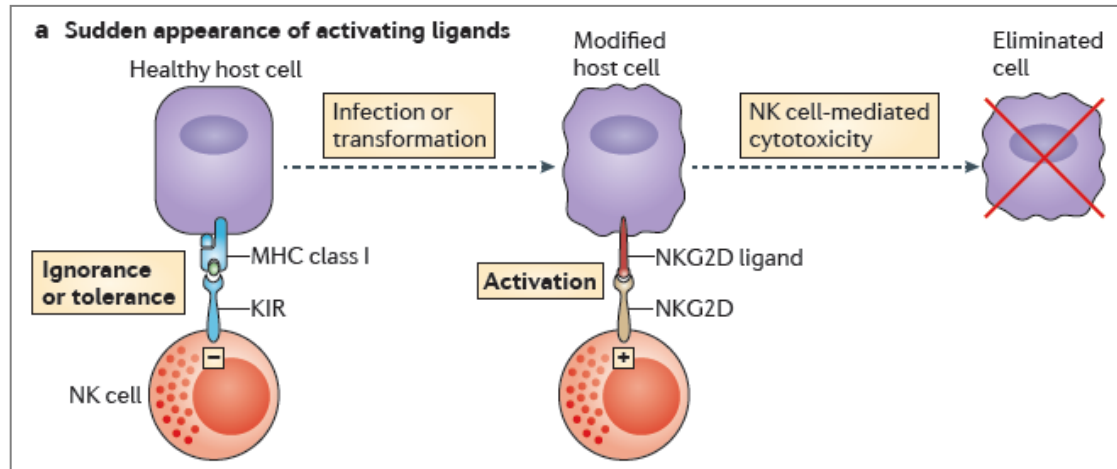
Response

- ORR : 65%
- CR : 40%

- Seven relapse. Median : 8.8 months (range 5-32 mo)
- Five patients have been allografted in CR/PR, including two who relapsed after SCT



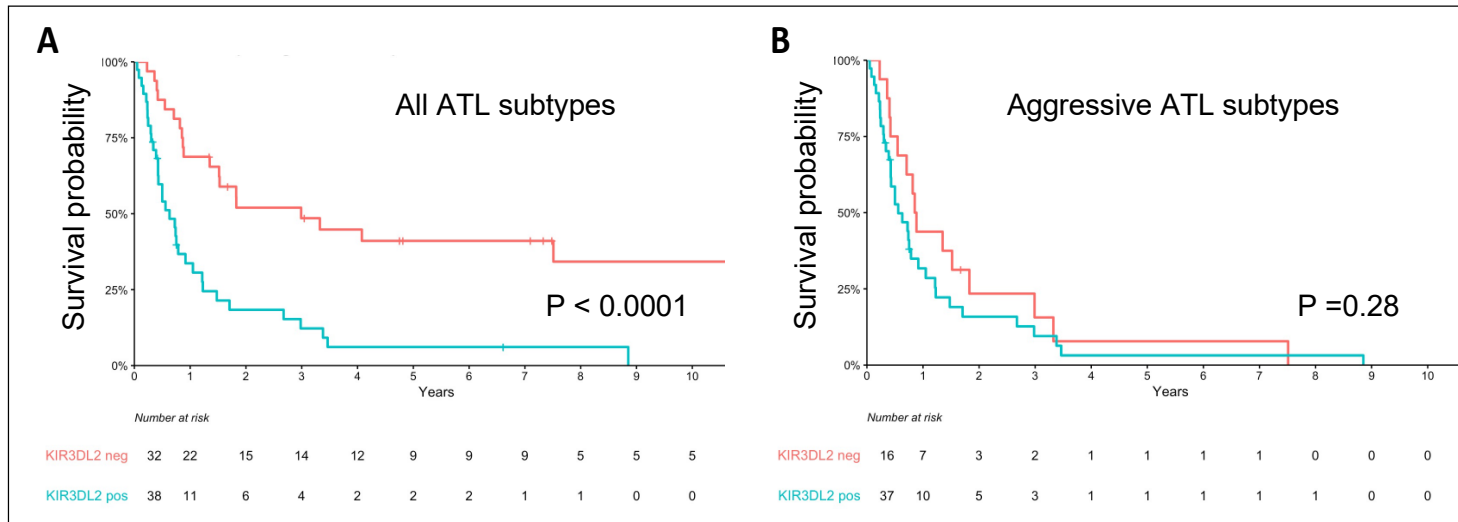
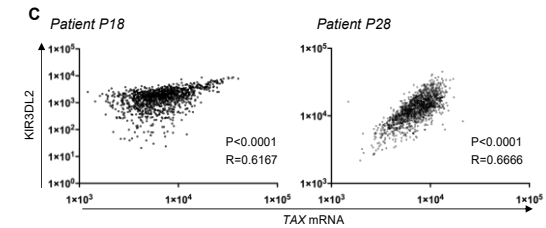
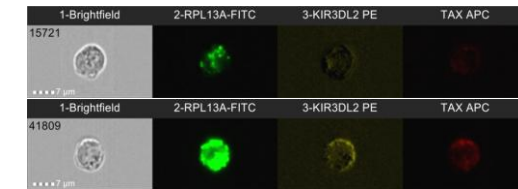
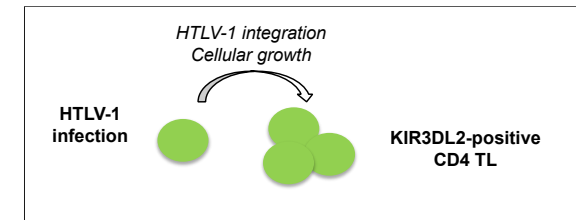
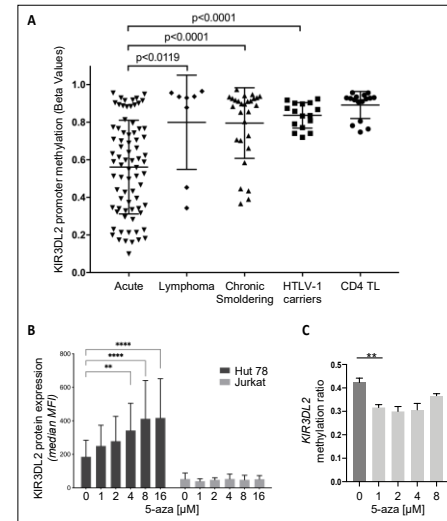
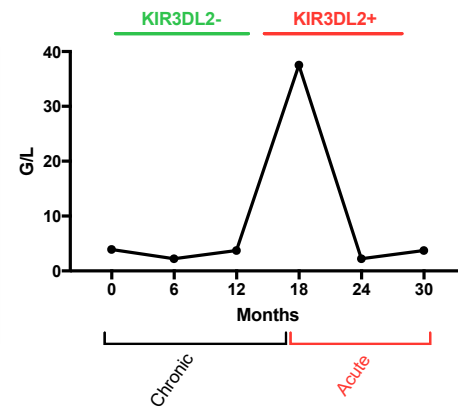
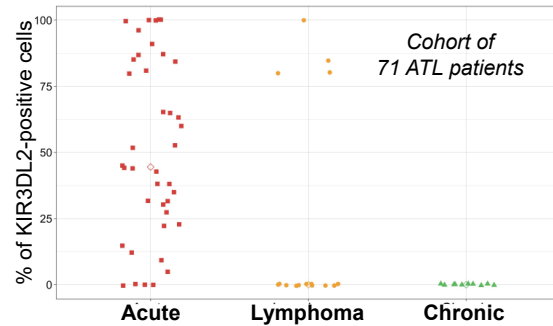
Transdifferentiation with loss of Bcl11b expression and NK-like reprogramming in chronic stimulation of T cells : Syk dependancy ?



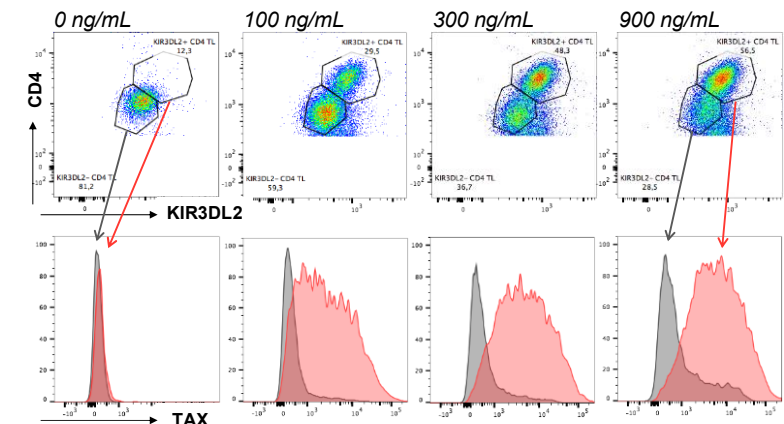
*Model of homeostatic proliferation (TCR-stim, cytokines)
Mature T cells from p53-deficient mice were transferred into
Cd3e-deficient mice (which lack mature T cells)*

KIR3DL2 is a novel diagnostic marker of acute-type ATL

NK receptors screen in a discovery cohort of 21 ATL → Expression of KIR3DL2

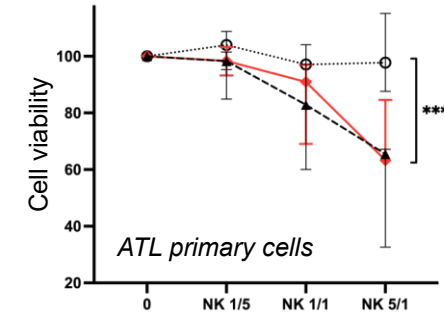
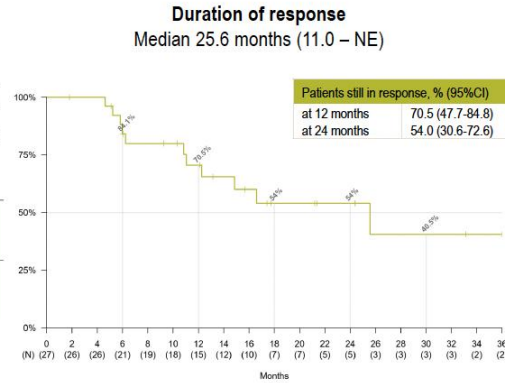
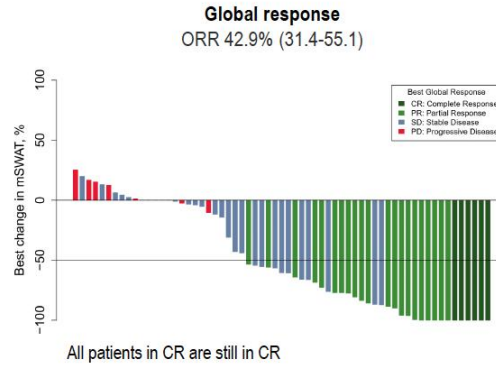


HTLV-1 p19

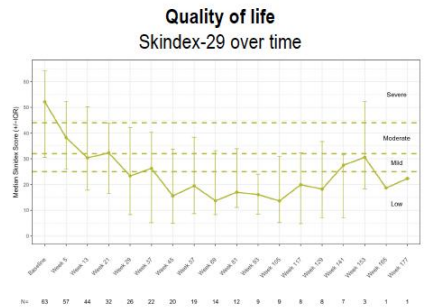


Lacutamab in heavily pretreated SS patients

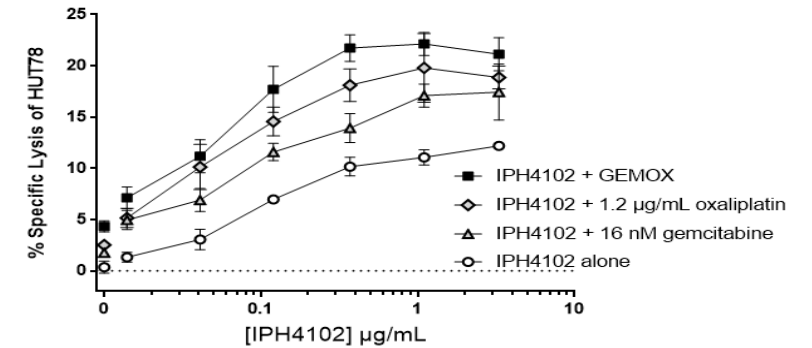
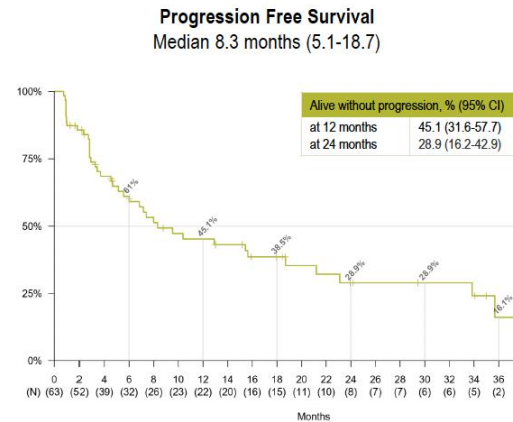
ORR 43%



DOR 25.6 months

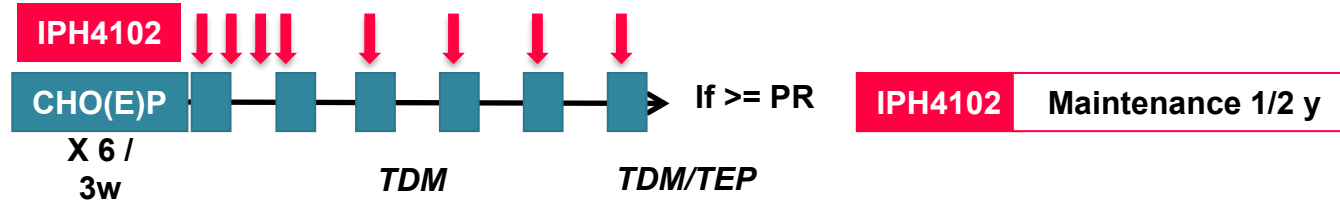


- Early decrease of skindex-29 score starting from W5 from severe (baseline) to moderate score
- Continuous and deep decrease to low score maintained over time
- Same trends observed for pruritus

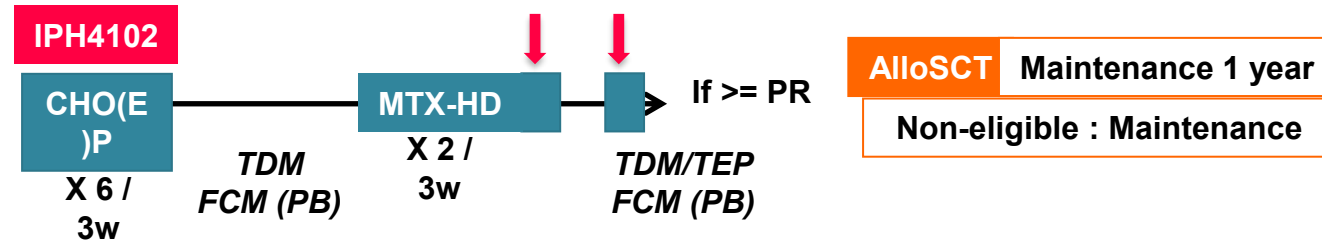


Study treatment

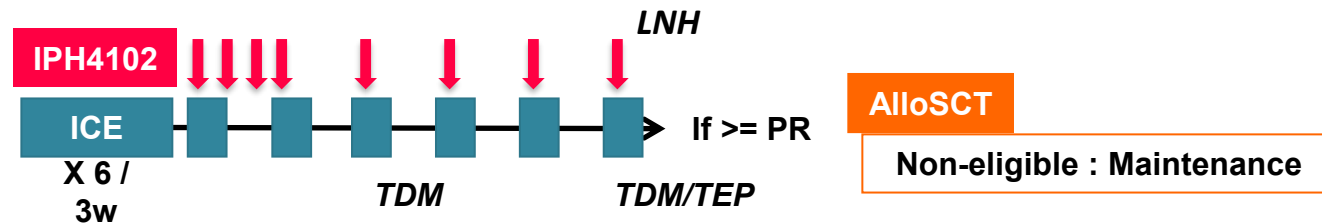
Cohort 1 : PTCL, nos & TFH PTCL (ALCL, ALK neg?)



Cohort 2 : ATL



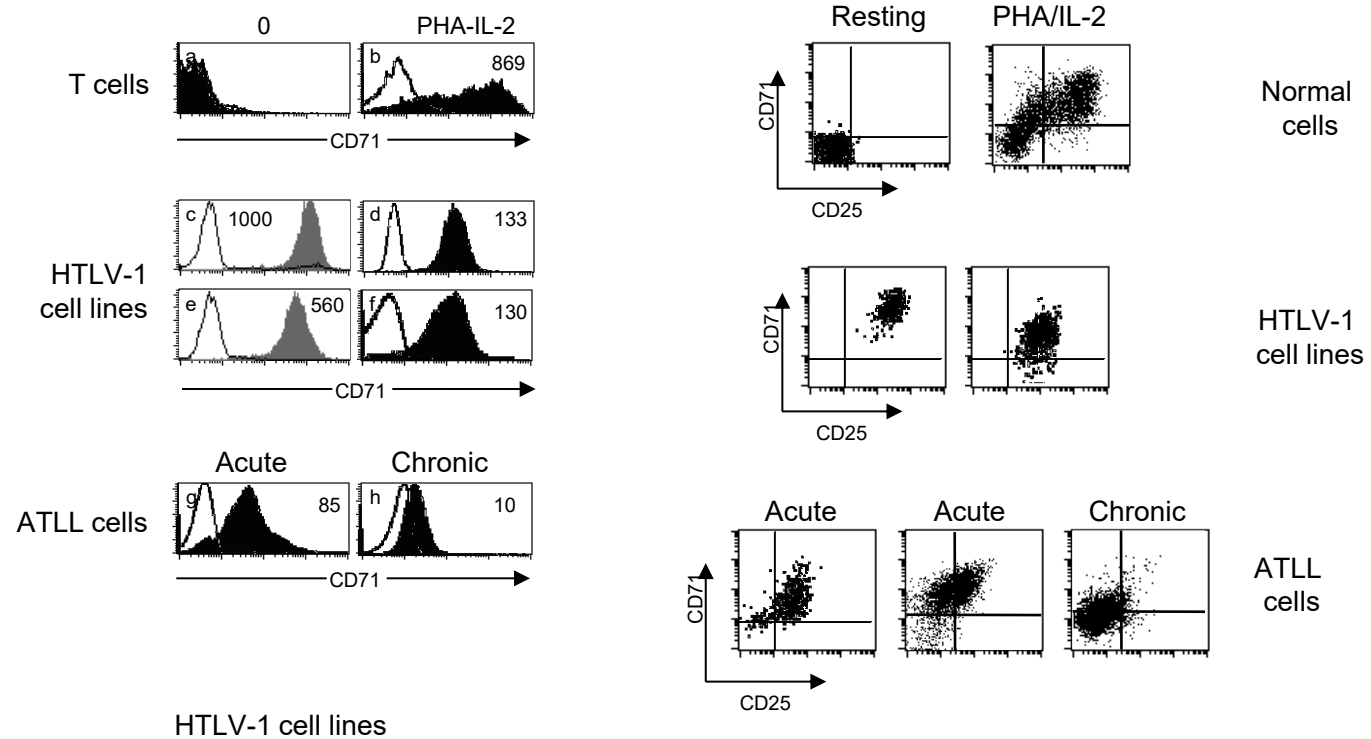
Cohort 3 : HSTL, MEITL, PCGD-TCL, primary cutaneous CD8+ aggressive epidermotropic



*Combinaison with demethyl agents
EZH1/2 inhibitors*

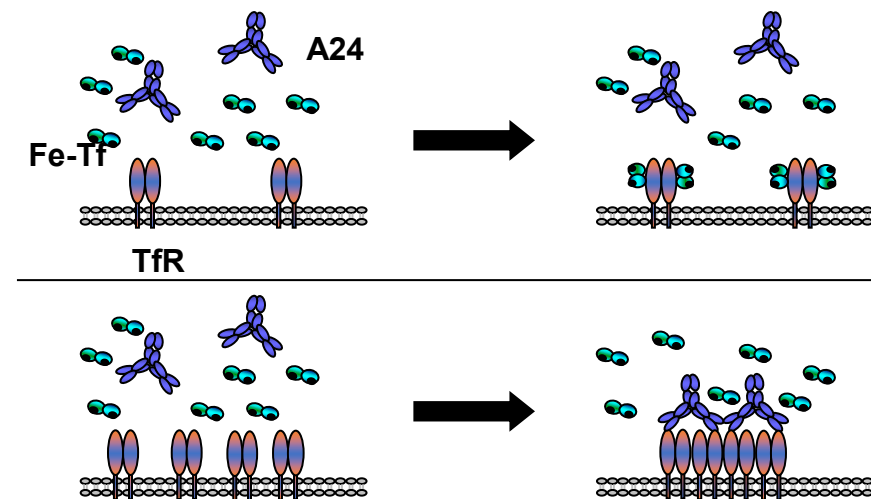
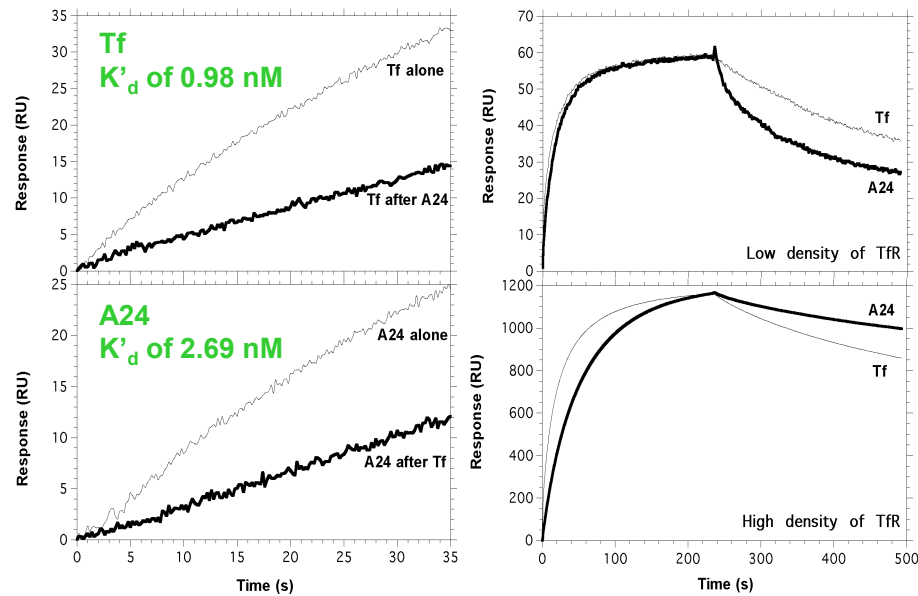
CAR-T cells (avoiding fratricidie)

TfR is highly expressed on ATLL cells



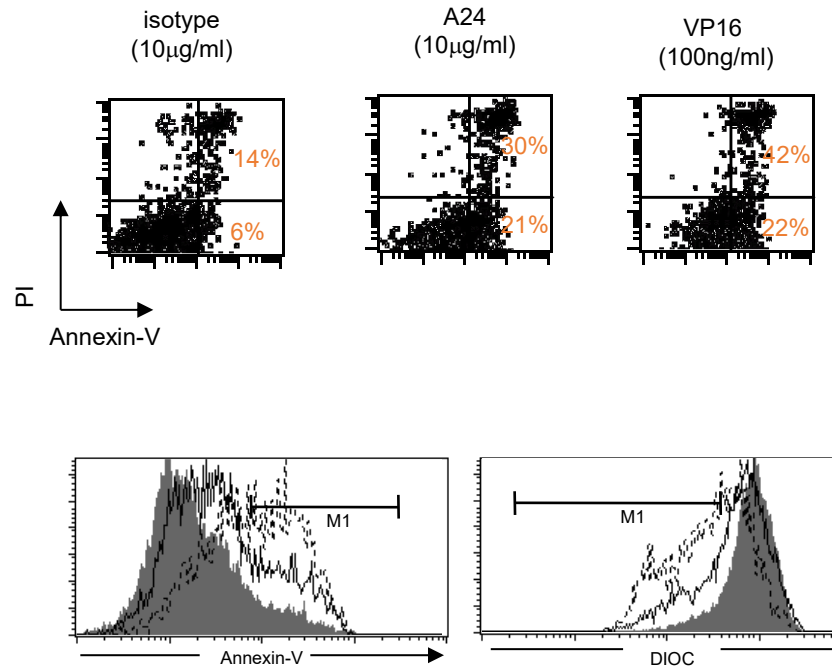
Moura et al Blood 2004, 103: 1838

A24 competes with Fe-Tf for receptor binding with higher affinity

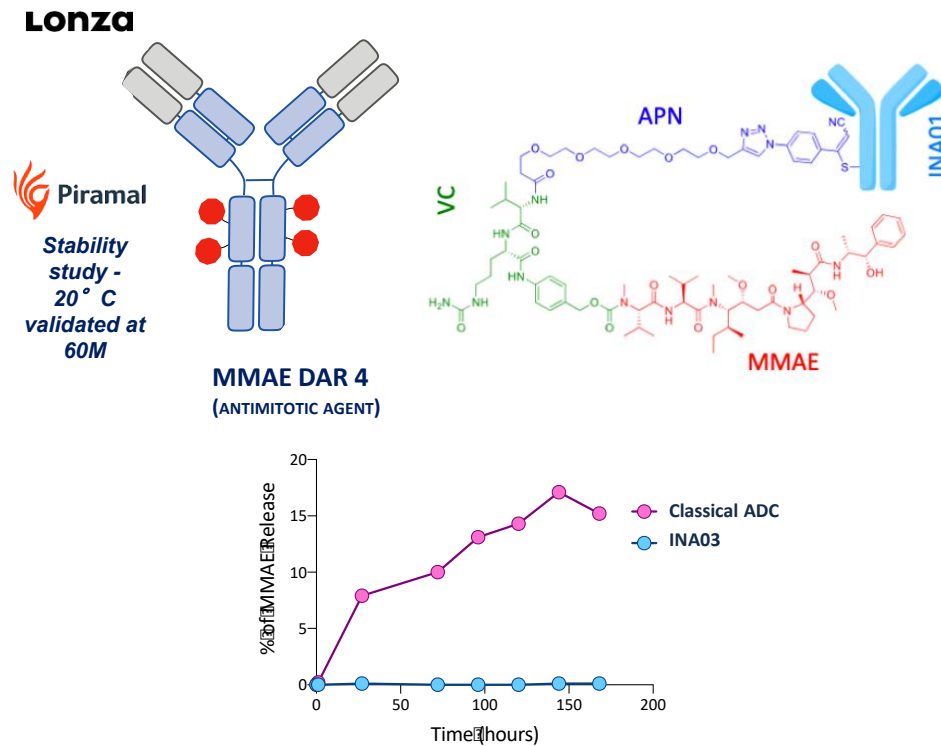


Moura et al, Blood, 2004

Mouse Anti-TfR antibody (A24) induces apoptosis of ATLL cells through mitochondrial depolarization (proof of concept)

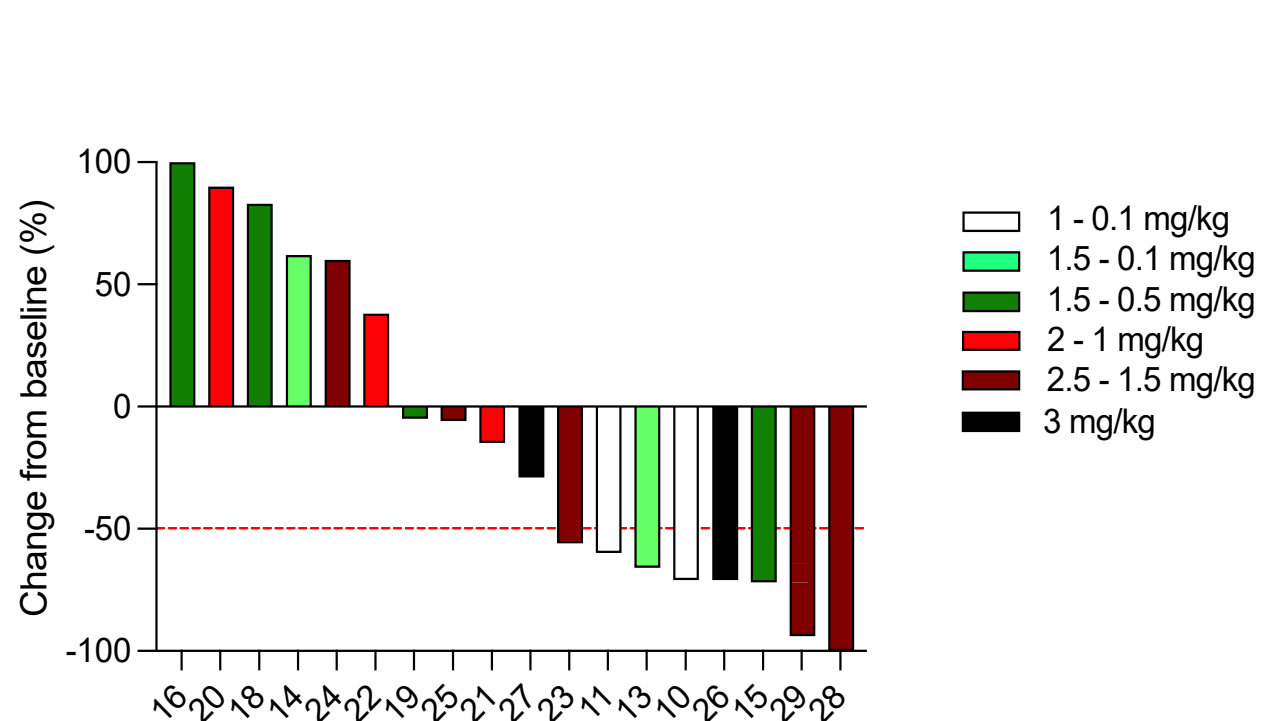


INA03 conjugate with MMAE (ADC)



- The APN group is different from the classical maleimide group
- This linker is more stable, leading to less toxicity
- The green part VC is a dipeptide valine-citrulline that is cleaved by enzymes within the cells, allowing a “bystander effect” of ADCs
- The red part of the payload is the cytotoxic MMAE, already used extensively clinically, including for Adcetris® – both efficacy and putative side effects of this drug are well characterized

Safety and RP2D in Human patients with acute leukemia (Phase 1)



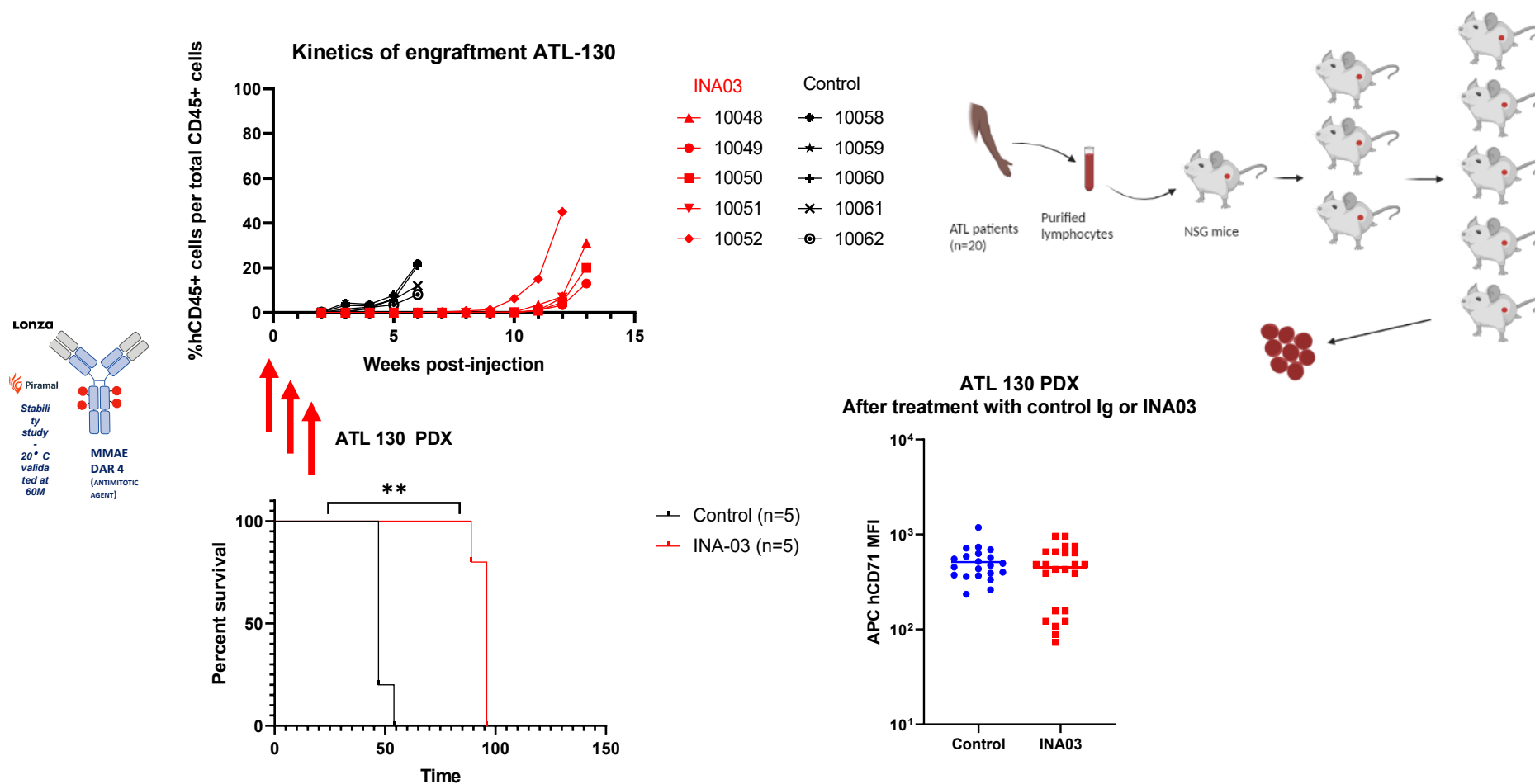
Adverse Events, n (%)*	Any grade AE	Grade ≥ 3 AE
Any AEs	29 (100)	25 (86)
FEBRILE NEUTROPENIA	14 (48)	13 (45)
HEADACHE	13 (45)	0
NAUSEA	9 (31)	1 (4)
DIARRHEA	9 (31)	0
ORAL MUCOSITIS	8 (28)	4 (14)
CONSTIPATION	8 (28)	0
LOWER LIMBS EDEMA	6 (21)	0
FEBRILE APLASIA	6 (21)	6 (21)
IRR	6 (21)	0
ASTHENIA	5 (17)	0
VOMITING	5 (17)	0
SEPSIS	5 (17)	5 (17)
FALL	4 (14)	1 (4)
NEUTROPENIA	3 (10)	3 (10)
FEVER	3 (10)	1 (4)
ANXIETY	3 (10)	0
DYSPNEA	2 (7)	0
ABDOMINAL PAIN	2 (7)	0
CONFUSION	2 (7)	1 (4)
ALOPECIA	2 (7)	0
ATRIAL FIBRILLATION	2 (7)	0
BONE PAIN	2 (7)	0

* AE occurring in ≥ 7% of patients regardless of cause

Blasts reductions at **more than 50%** were seen in **9/20** evaluable patients at the doses > 1 mg/kg

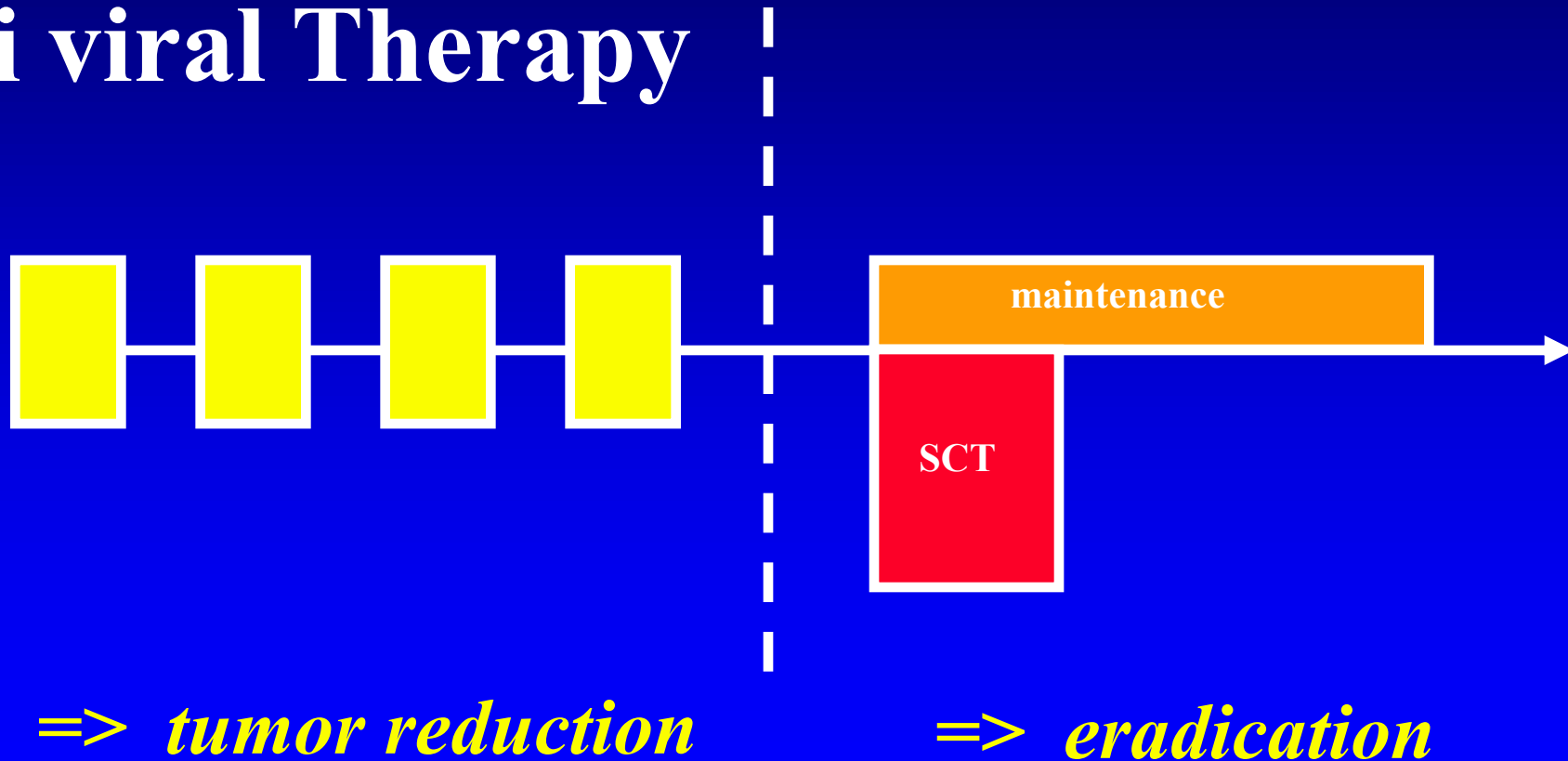
INA03 prevents development of ATLL in a PDX models

Collaboration with Pasteur Institute (A3 facility)



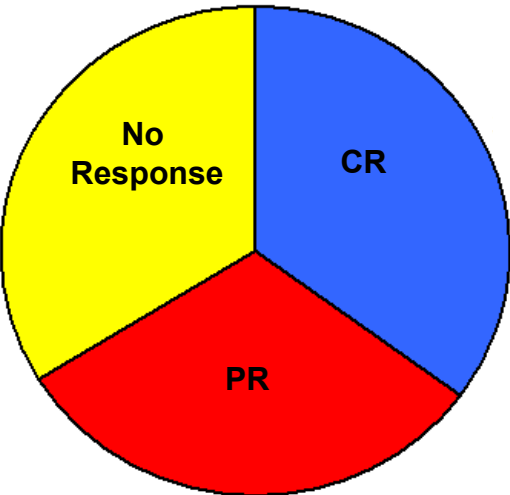
Optimal treatment of ATL

Anti viral Therapy

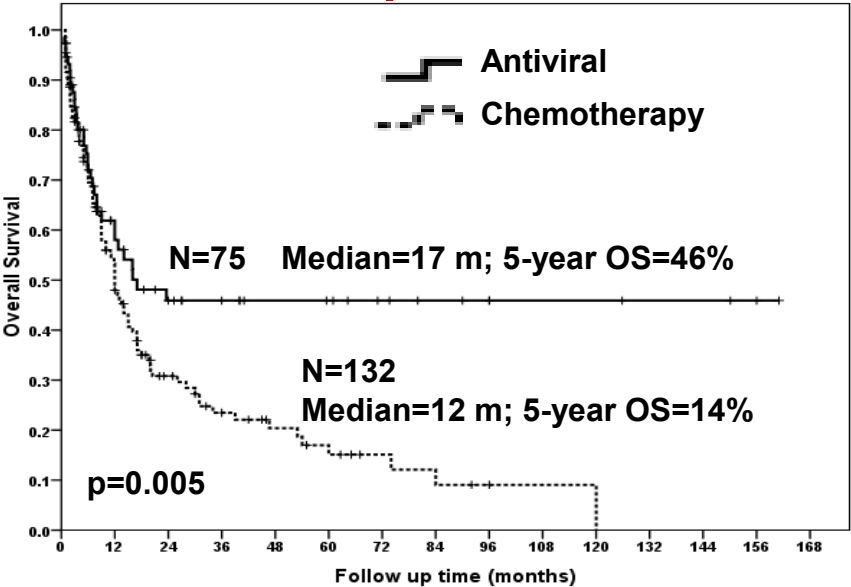


Worldwide meta-analysis: zidovudine + interferon-α

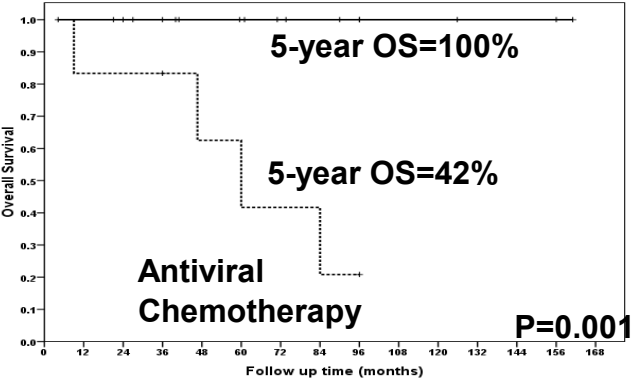
Response to first line antiviral therapy



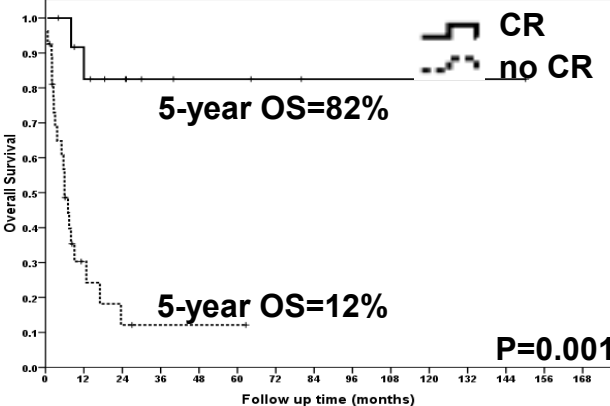
All patients



Smoldering/chronic ATL

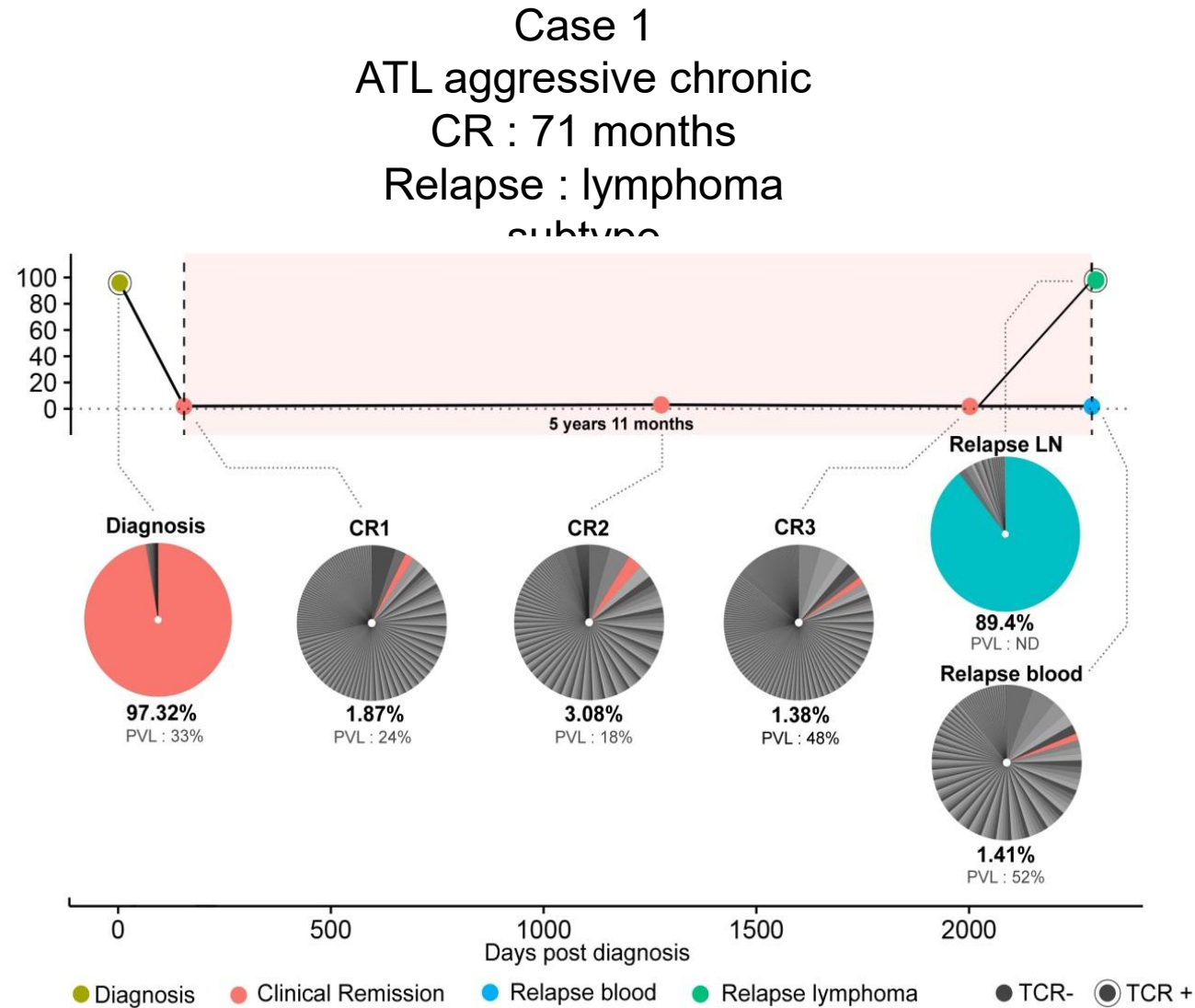


CR effect in acute ATL



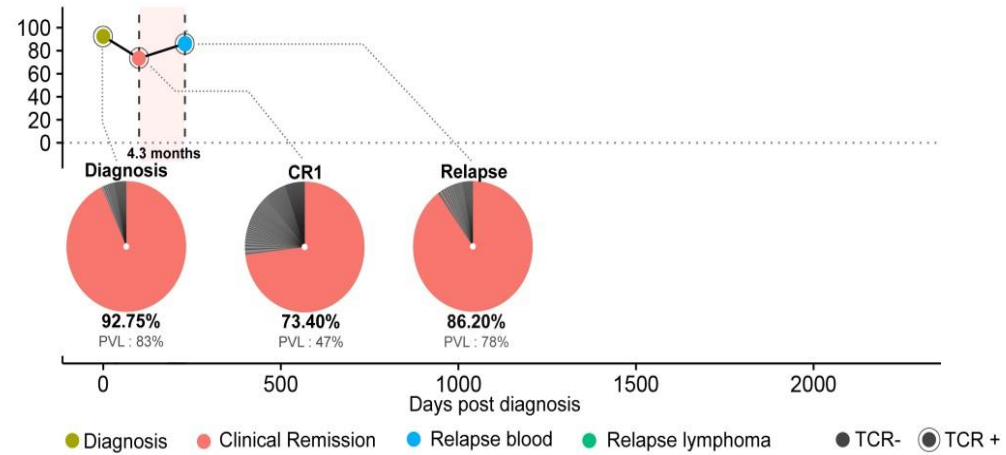
Variables	Multivariate analysis		
	P value	Adjusted Hazard Ratio	95% CI
First line therapy (Chemotherapy alone)			
Antiviral alone	0.021	0.55	(0.33, 0.91)
Chemotherapy then antiviral	0.083	0.68	(0.44, 1.05)

Timeline of long term responder patients

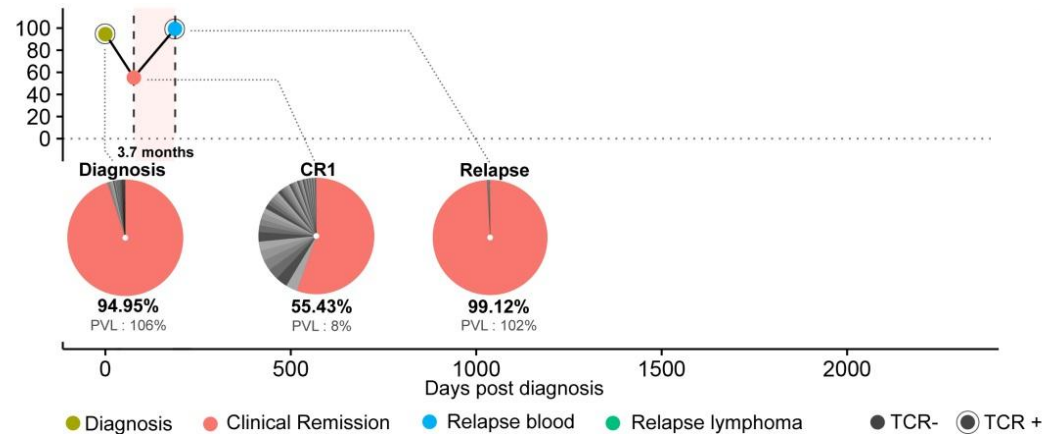


Timeline of short term responder patients

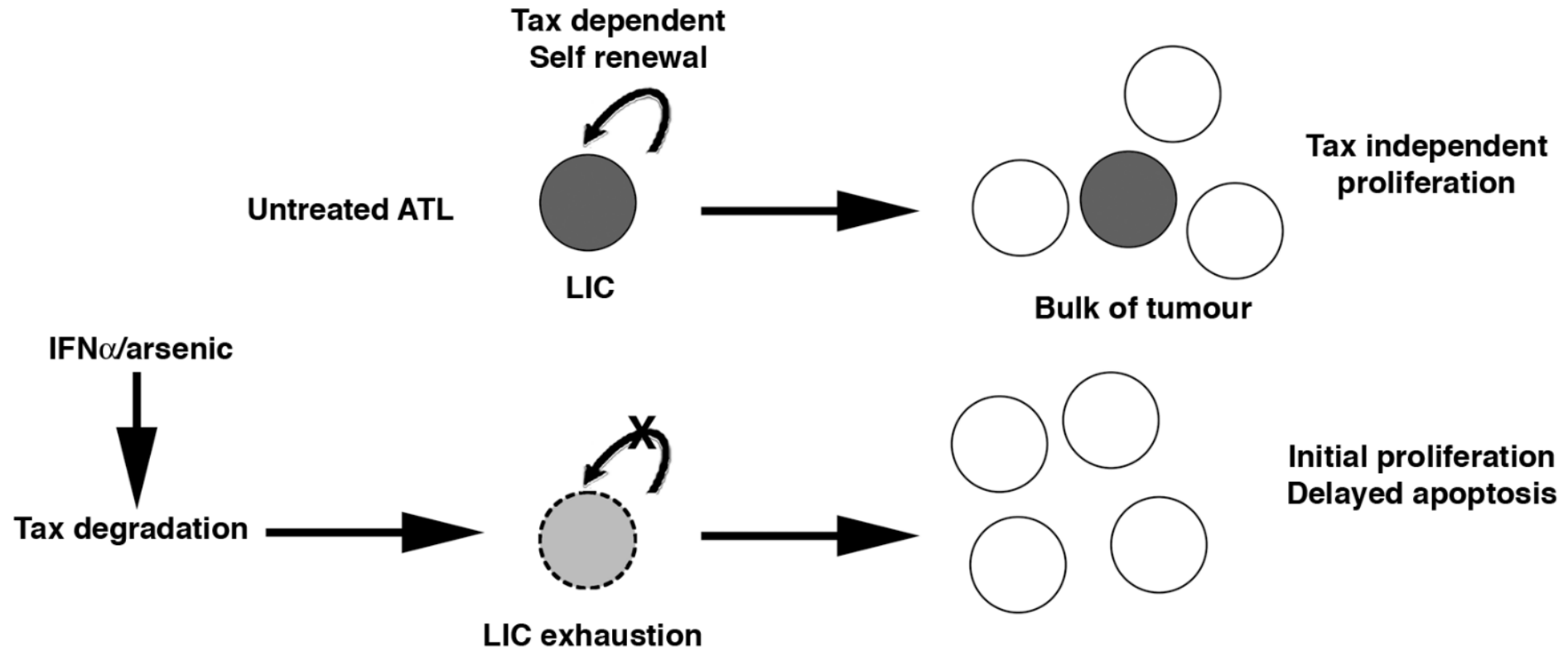
Case 4
Acute subtype
CR: 4,3 months



Case 5
Acute subtype
CR: 3,7 months



Proposed model



Arsenic/IFN/AZT induce CR and prolong survival in ATL

blood

2009 113: 6528-6532
Prepublished online May 1, 2009;
doi:10.1182/blood-2009-03-211821

Phase 2 study of the efficacy and safety of the combination of arsenic trioxide, interferon alpha, and zidovudine in newly diagnosed chronic adult T-cell leukemia/lymphoma (ATL)

Ghada Kchour, Mahdi Tarhini, Mohamad-Mehdi Kooshyar, Hiba El Hajj, Eric Wattel, Mahmoud Mahmoudi, Hassan Hatoum, Hossein Rahimi, Masoud Maleki, Houshang Rafatpanah, S. A. Rahim Rezaee, Mojtaba Tabatabaei Yazdi, Abbas Shirdel, Hugues de Thé, Olivier Hermine, Reza Farid and Ali Bazarbachi

Response and follow up of patients after Arsenic/AZT/IFN

Patient	Response at last follow up	Survival (months)	Survival status
1	CR	15+	Alive
2	CR	15+	Alive
3	VGPR*	12+	Alive
4	CR	10+	Alive
5	CR	8+	Alive
6	CR	3+	Alive
7	CR	8+	Alive
8	CR	4+	Alive
9	VGPR**	5+	Alive
10	PR***	2+	Alive

* 8% atypical lymphocytes on peripheral blood smear

** 6% atypical lymphocytes on peripheral blood smear

*** lymphocytosis decreased from 185000 to 6400

Skin lesions



Before



2 weeks



4 weeks

Follow up of ATL patients after stopping treatment in complete remission

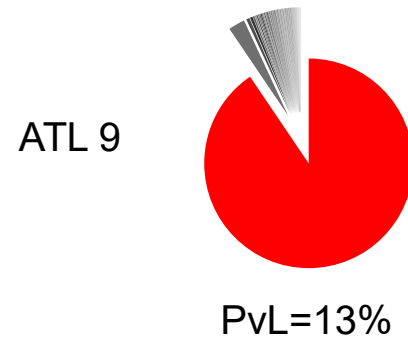
Subtype	Treatment	Follow up after stopping treatment
Chronic	IFN/AZT	Prog 1m
Chronic	IFN/AZT	Prog 3m
Acute	IFN/AZT	Prog 3m
Lymphoma	IFN/AZT	Prog 5m
Chronic	IFN/AZT	Prog 11m
Chronic	Arsenic/IFN/AZT	Prog 1m
Chronic	Arsenic/IFN/AZT	Prog 6m
Chronic	Arsenic/IFN/AZT	CCR after 7m follow up
Chronic	Arsenic/IFN/AZT	CCR after 7m follow up
Chronic	Arsenic/IFN/AZT	CCR after 7m follow up
Chronic	Arsenic/IFN/AZT	CCR after 18m follow up

Arsenic consolidation: The Necker Experience

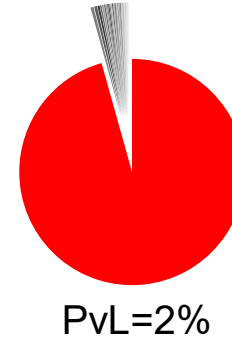
Patient	Sex	Age at diagnosis	Clinical subtype	P53 activity	First line treatment	Interval first therapy and As ₂ O ₃ (M)	Disease status at time of A ₂ So ₃	Treatment duration (weeks)	OS since diagnosis (M)	Death	OS since arsenic (M)	Duration of response since arsenic (M)	Prog
ATL 6	M	51,6	Chronic	F	AZT-IFN-VP16	24,4	SD	4	53	Yes	28	22	Yes
ATL 7	F	59,8	Acute	F	CHOP like	6,2	PD	4	8	Yes	1	NA	Yes
ATL 9	M	50,6	Chronic	F	CHOP like	20,1	CR	6	48	Yes	28	25	Yes
ATL 11	M	27,7	Chronic	F	LSG 15+ AZT-IFN	13,2	VGPR	6	84	No	70	70	No
ATL 14	F	35,1	Acute	NF	Alemtuzumab-CHOP	2,2	CR	4	12	Yes	10	5	Yes
ATL 43	F	66,3	Lymphoma	F	CHOP like	6,3	CR	8	19	Yes	12	5	Yes
ATL 44	F	54,8	Lymphoma	F	CHOP like	3,8	VGPR	8	36	Yes	32	29	Yes
ATL 64	M	63,1	Lymphoma	ND	CHOP	13	CR	8	47	No	34	34	No
ATL 65	M	54,4	Lymphoma	ND	CHOP/DHAox	4	PR	16	36	No	31	10	Yes

**Relative abundance of the dominant unique integration site (UIS; red)
within total proviral UIS before and after Arsenic-IFN-AZT treatment**

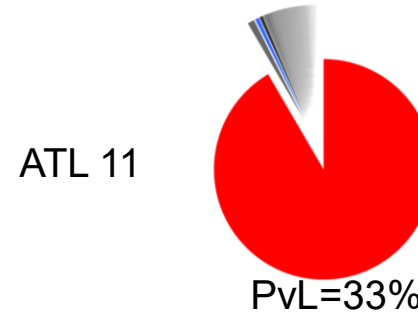
January 2009: Pre arsenic



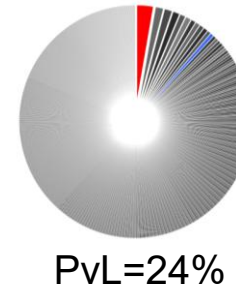
June 2009: Post arsenic



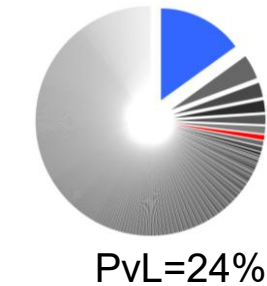
March 2010: Pre arsenic



August 2010: Post arsenic



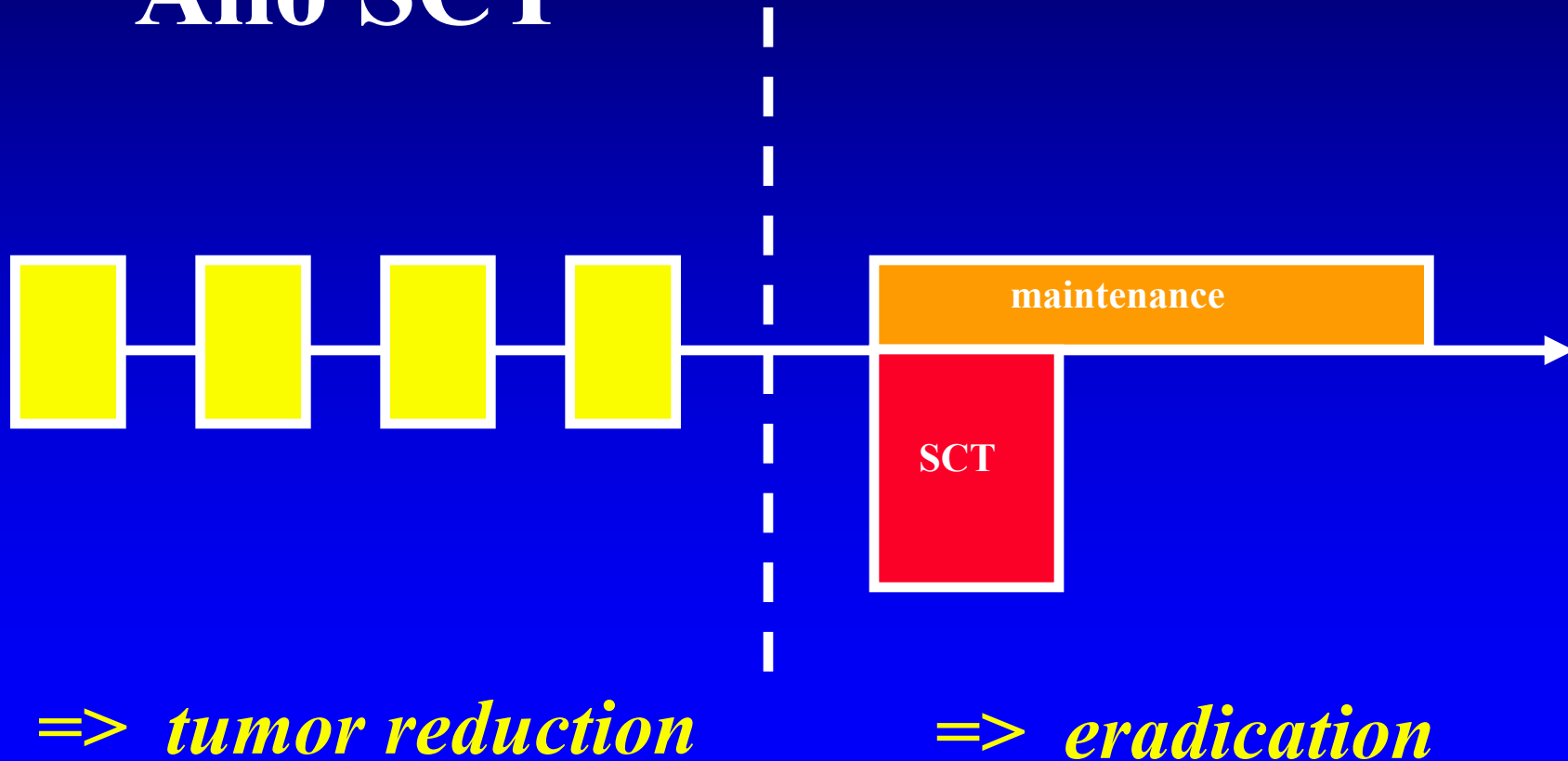
June 2012 CR



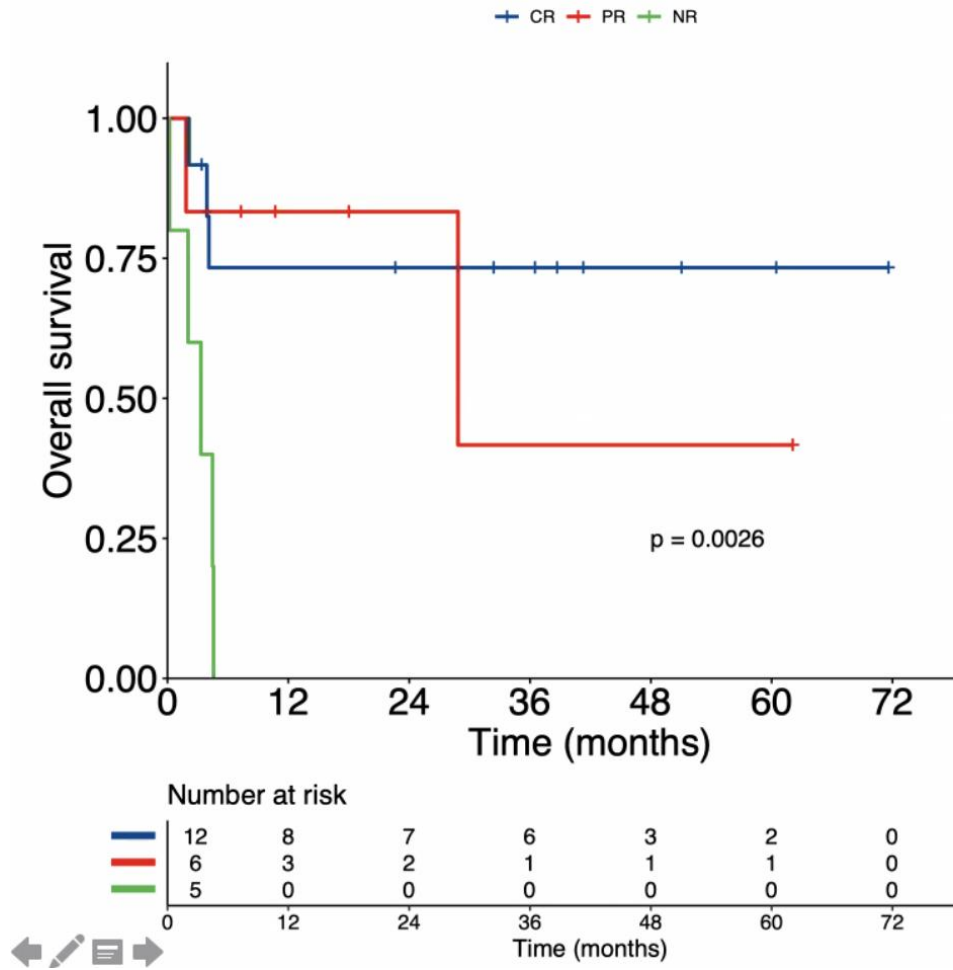
Marcais al. Retrovirology 2020

Optimal treatment of ATL

Allo SCT



Outcome: overall survival (OS)



Survival according to disease status at time of alloSCT	OS at two years	Median
CR	73% [51-1]	Not reached
PR	83% [58-1]	Not reached
SD/PD	0%	3 months

Cause of death

- Intestinal acute GVHD (n=2)
- MOF (n=1) and hepatic failure (n=)
- Progression/relapse (n=6)

Dedicated HTLV-1 follow-up

Proviral load quantification (n=13 patients)

→ Negative proviral load in 12/13 (mean 60 days)

→ Two patients reverted to positive PvL at 12 and 30 months (PvL <1%), respectively while sustaining full donor chimerism.

→ One patient PvL : 0.2%, chimerism recipient : 0.11%

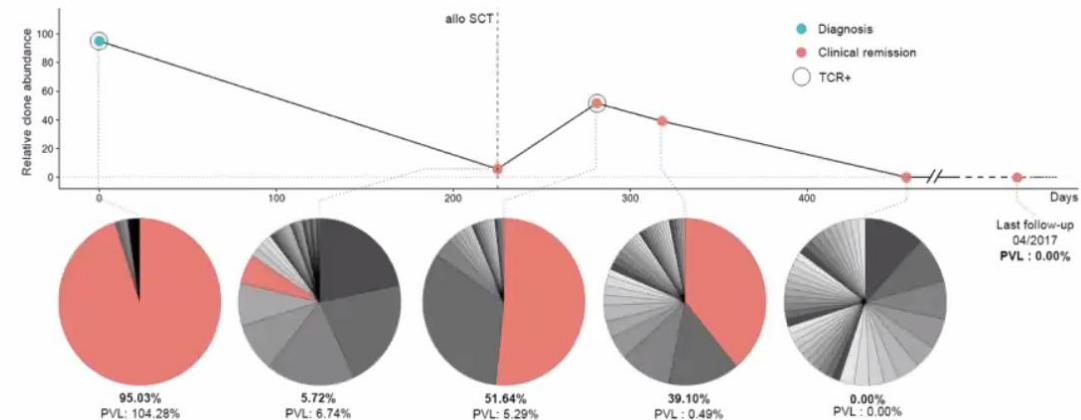
Clearance of the tumor viral clone assessed with HTS in leukemic subtypes

42 year old female

chemotherapy with BV-CHP et MTX HD→

partial remission

Allogeneic HSCT with MSD (HTLV-1 negative)



Allogeneic haematopoietic cell transplantation in PTCL: recommendations from the EBMT Practice Harmonisation and Guidelines Committee



Adult T-cell leukaemia lymphoma

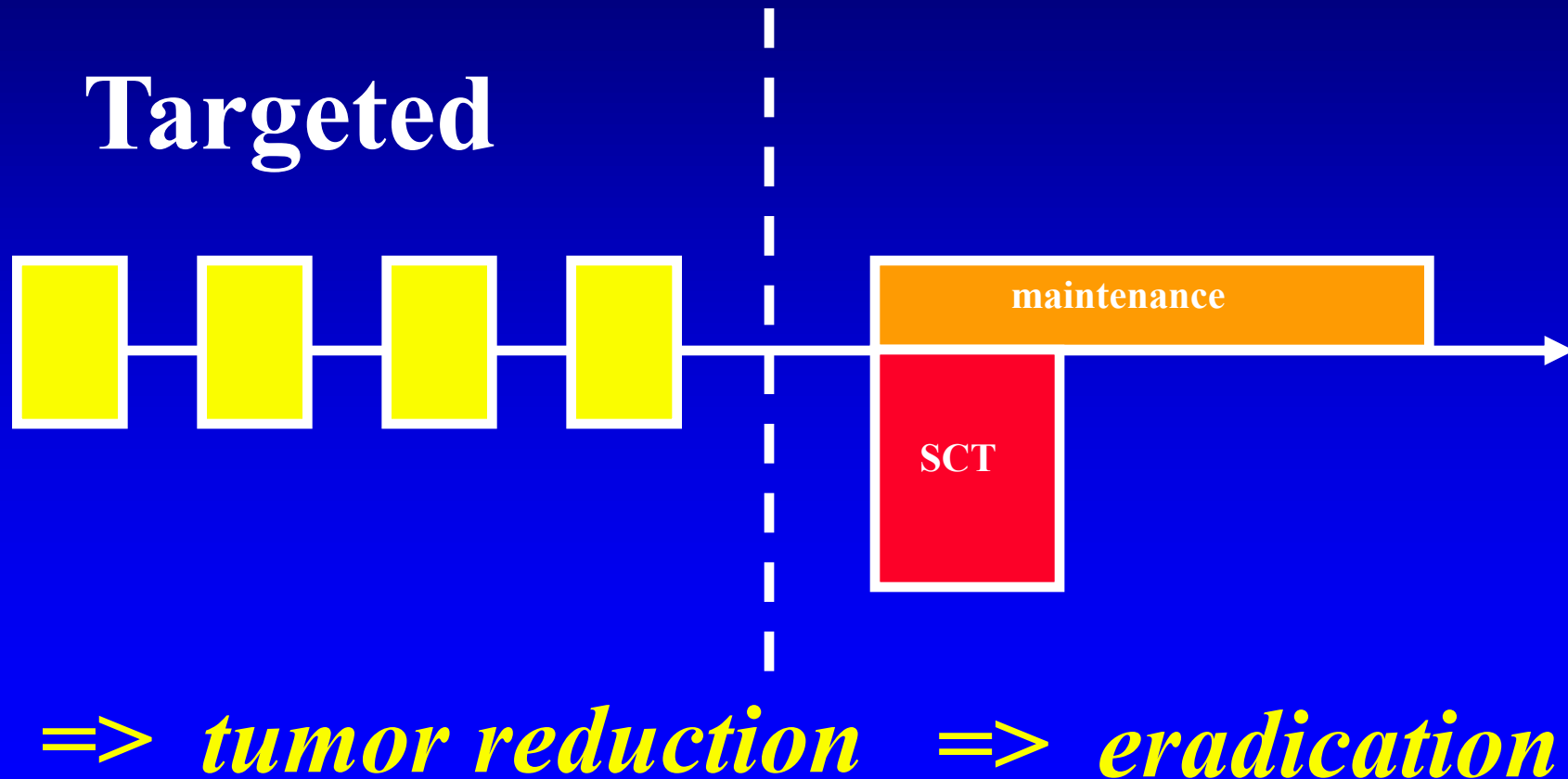
- Assess eligibility for allo-HCT and consider donor search at diagnosis
- Allo-HCT should be considered as a **first-line treatment option as soon as CR, PR, or SD is reached**
- If allo-HCT not done in first-line, its use in R/R situations should be considered
- Pre-tHCT moga should be avoided because of an increased risk of GVHD.
- BV-based therapies are recommended for CD30-positive cases
- Autologous HCT should not be proposed.
- RIC preferable and HTLV-1 negative donors are preferred.
- Donor selection: follows general recommendations, **including haplo** (BM vs PBMC, T1B1F)
- There is no standard post-transplantation maintenance.

Management of post-transplant relapse

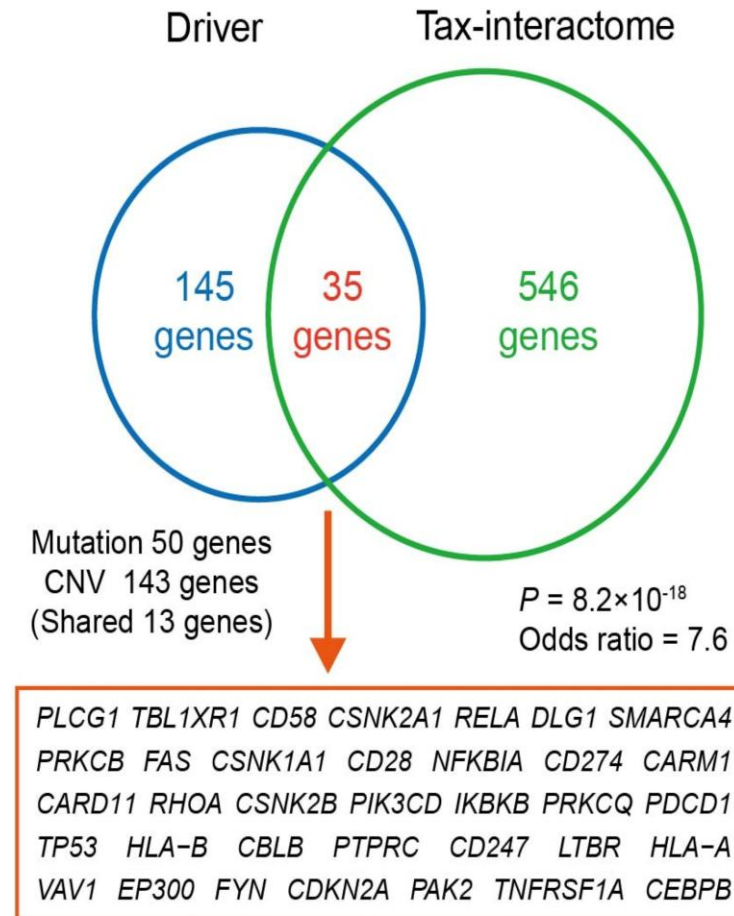
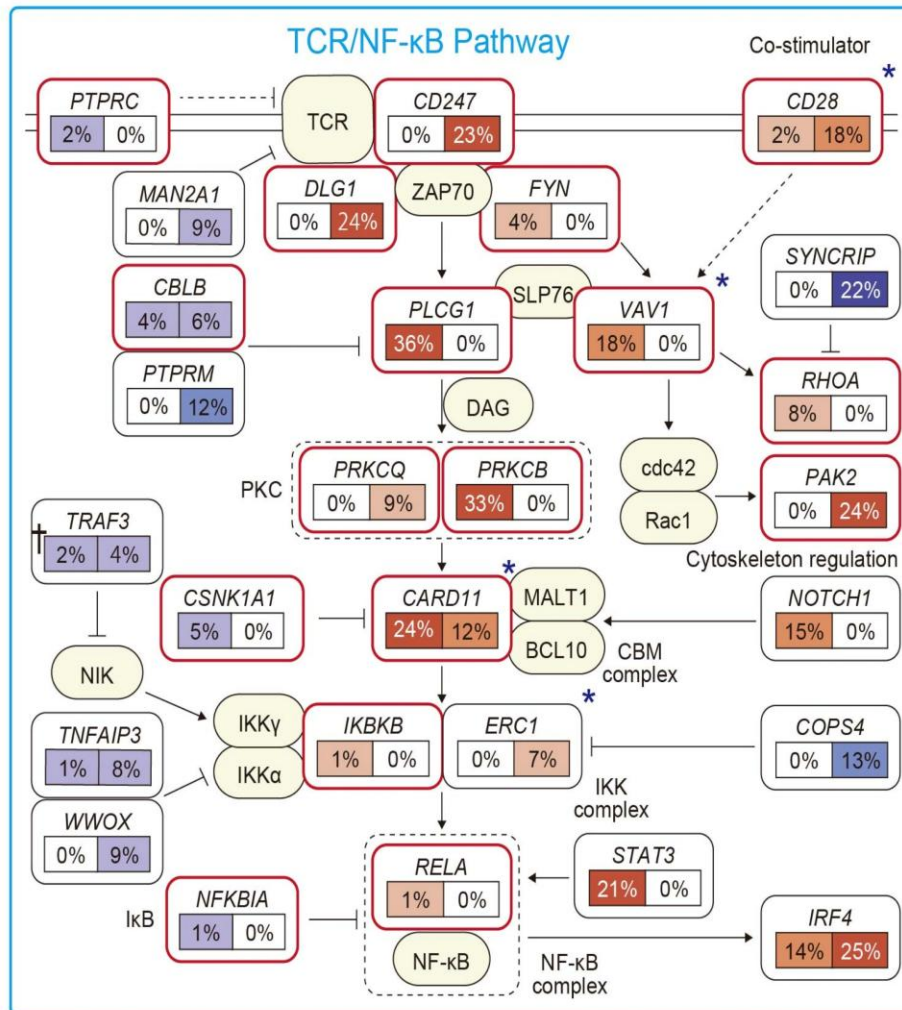


- Clinical trial
- Donor lymphocyte infusion
- Lenalidomide (increase GVL)
- Valemestostat (increase expression of virus and increase GVL)
- Mogamulizumab (reduce Treg induced GVL +JAK2i (prevention of GVHD and IL-10 signaling) ?
- Zidovudine and interferon alfa or Dolutegravir (DTG) and Tenofovir (TDF): to prevent donor T cell infection
- Single agent chemotherapy such as etoposide
- Anti-PD-1 or anti-PD-L1 antibody treatment should be avoided, at least in monotherapy, to prevent the high risk of flare-up and GVHD.

Optimal treatment of ATL



Mutations Landscape in ATLL



New agents (T cell lymphoma ?)

- Bendamustine
- Pralatrexate
- Proteasome inhibitors
- Deacetylase Inhibitors
- Demethylating agents
- **EZH2 inhibitors** (approved in Japan for relapsed disease)
- MCL-1 inhibitors and antiretrovirals
- **Lenalidomide** (approved in Japan for relapsed disease)
- SYK inhibitors

HDAC Inhibitors and Other Targeted Agents

Tucidinostat (chidamide) — HDAC inhibitor, oral

Phase II (n=23 R/R post-moga + chemo): ORR 30%, median PFS 1.7 months, OS 7.9 months

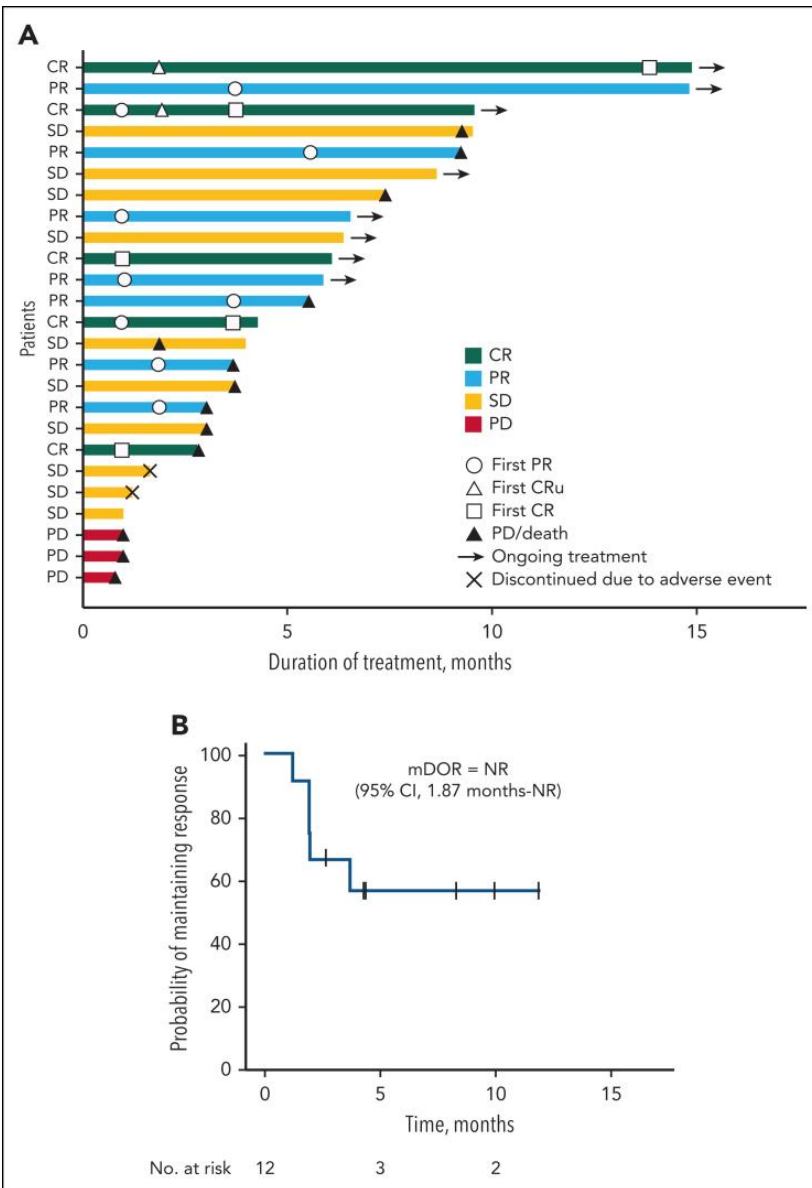
Modest activity; consider positioning before valemestostat (epigenetic overlap)

Belinostat + AZT ± IFN- α (NCT02737046, Phase II)

Interim data (n=6): complete molecular CRs in subset; PVL undetectable

Rationale: HDAC inhibition + viral suppression + immune activation

Valemetostat (DS-3201): First Epigenetic Therapy Approved for ATL



Mechanism: Dual EZH1/EZH2 inhibitor → reverses polycomb-mediated transcriptional silencing of tumor suppressors

Phase II Japan (Yoda et al., Lancet Oncol 2022, n=25 R/R ATL)

ORR 48%, CR 20%; median PFS 7.4 months; median OS 16.4 months

Tolerability: thrombocytopenia 58%, dysgeusia 50%, alopecia 42% (TEAEs)

Lenalidomide: Immunomodulatory Agent in ATL

Mechanism: CRBN-mediated Ikaros/Aiolos degradation; T-cell co-stimulation; anti-angiogenesis; NK activation

Oral agent with CNS penetration — relevant given CNS tropism of ATL

Phase II Japan (Ogura et al., JCO 2016, n=26 R/R ATL)

ORR 42%; median PFS 3.8 months; median OS 20 months

73% stable disease or better; manageable toxicity profile

NCCN-listed for R/R ATL (2L+ option)

Geographic heterogeneity: US Phase II closed early (0% ORR in 4 patients enrolled)

Suggests biological or genetic differences between Japanese and Western ATL cohorts

Ongoing: NCT04301076 — Lenalidomide + EPOCH (NCI, untreated aggressive ATL)

Combinations under study: lenalidomide + mogamulizumab; lenalidomide + BV

MCL-1 Inhibitors: Exploiting Apoptosis Dependency

Rationale: ATL cells overexpress MCL-1 (anti-apoptotic BCL-2 family) → MCL-1 addiction

BCL-2 inhibition (venetoclax) less effective in T-cell malignancies; MCL-1 is the key dependency

Preclinical breakthrough (Cell, 2025, HTLV-1c model)

MCL-1 inhibitors selectively destroy HTLV-1-infected cells in vitro and in vivo

TDF + DTG + MCL-1i combination: further delayed disease progression vs antiretrovirals alone

Suggests rational triple combination for early/preventive intervention

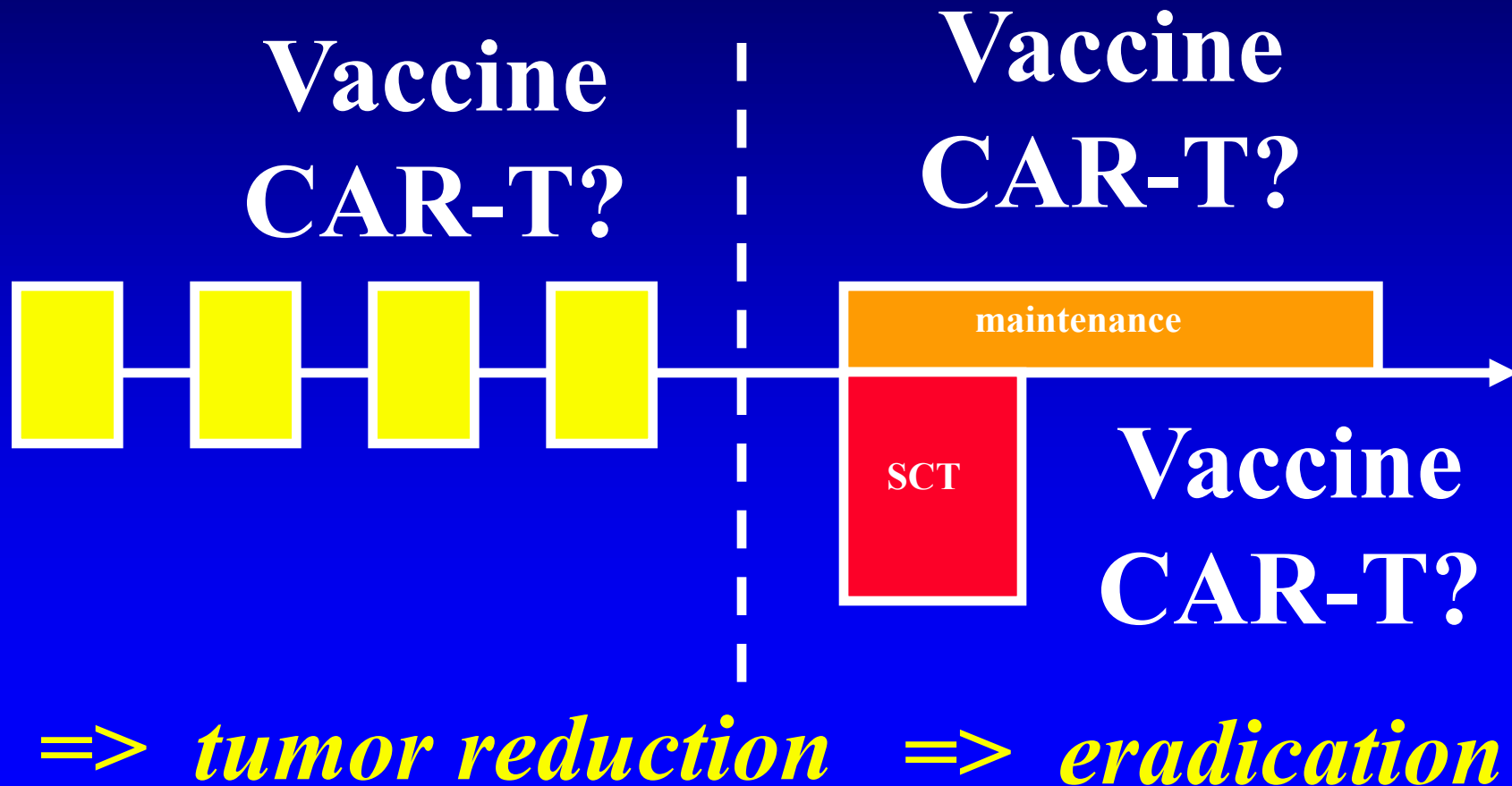
Clinical-stage MCL-1 inhibitors

AZD5991 (AstraZeneca) — Phase I in hematologic malignancies (Clin Cancer Res 2024): first-in-human; MDS responses; ATL not specifically enrolled

S64315/MIK665 — Phase I hematologic malignancies (ongoing)

Critical next step: dedicated ATL/HTLV-1 Phase I cohort for MCL-1 inhibitors

Optimal treatment of ATL



CAR-T Cell Therapies: Emerging Cellular Immunotherapy for ATL

Unique challenge: ATL is a malignancy of CD4+ T cells → risk of targeting normal T cells + fratricide

CCR4-targeted CAR-T (NCI Phase I, ongoing)

Autologous CAR-T targeting CCR4 (highly expressed on ATL cells and Tregs)

Conditioning: Cy/Flu; dose escalation ongoing in CCR4+ mature T-cell malignancies including ATL

CD5 CAR-T — First-in-Human 2025

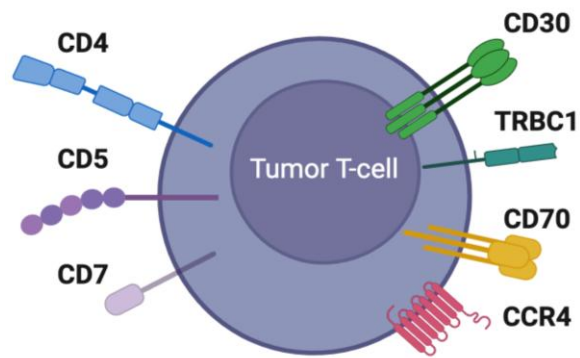
Single R/R ATL patient (49F, 5 prior lines), DL3: promising efficacy signal reported

Published 2025; larger cohort data awaited

CTX130 — Allogeneic anti-CD70 CAR-T (NCT04502446)

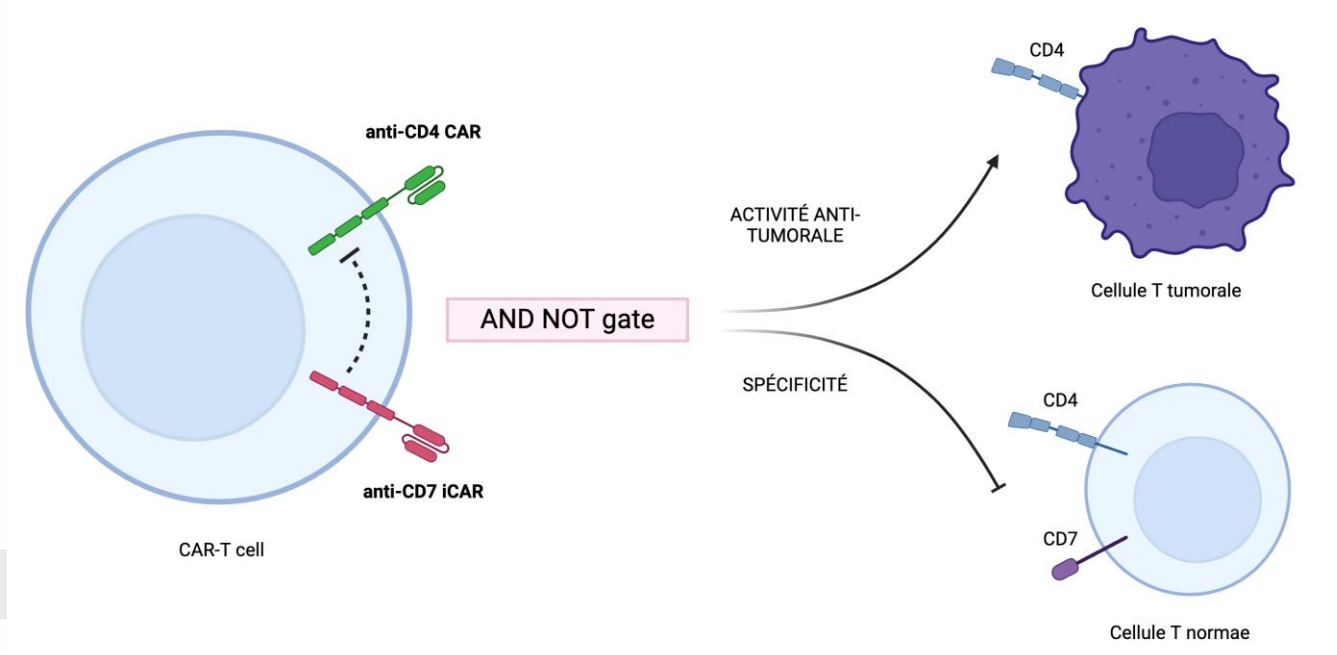
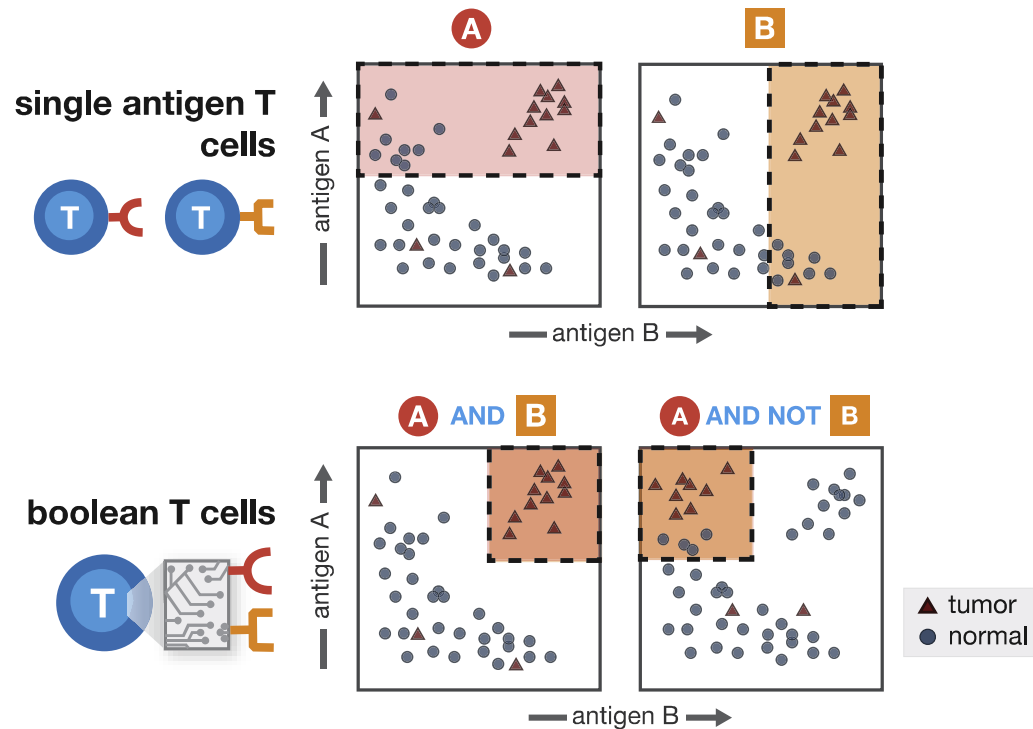
CRISPR-Cas9 edited allogeneic product; off-the-shelf availability

Interim 2024 results: activity in CD70+ T-cell malignancies



Key questions: fratricide risk, T-cell aplasia management, persistence in ATL microenvironment immune suppression (IL-10, TGF, PDL1, etc) and TKi

Double CAR-T cells CD4 positif, but inhibited by the CD7



Theravectys' lentiviral vector

Engineered from HIV, the lentiviral vector **only contains 18%** of the wild type HIV sequence and is:

Integrative

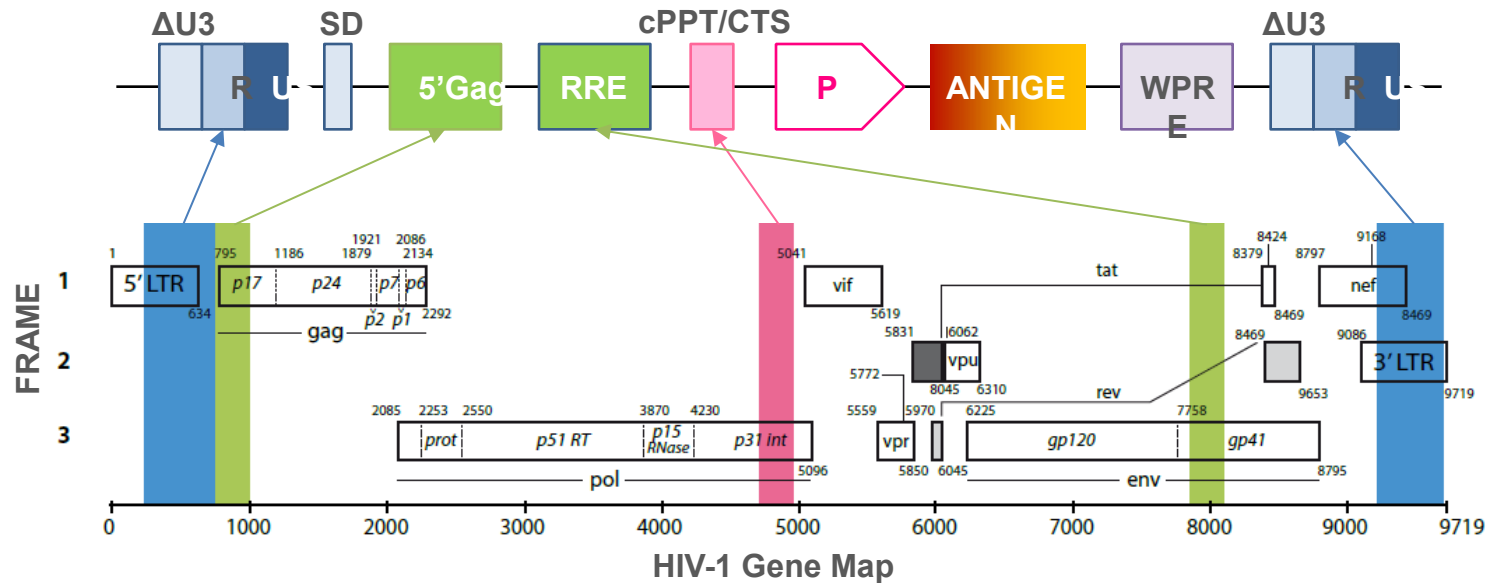
(as it contains the cPPT/CTS sequence also called DNA Flap)

Non replicative

(Δ U3 deletion in LTR promoter)

Non pathogenic

(all the virulence genes have been deleted)

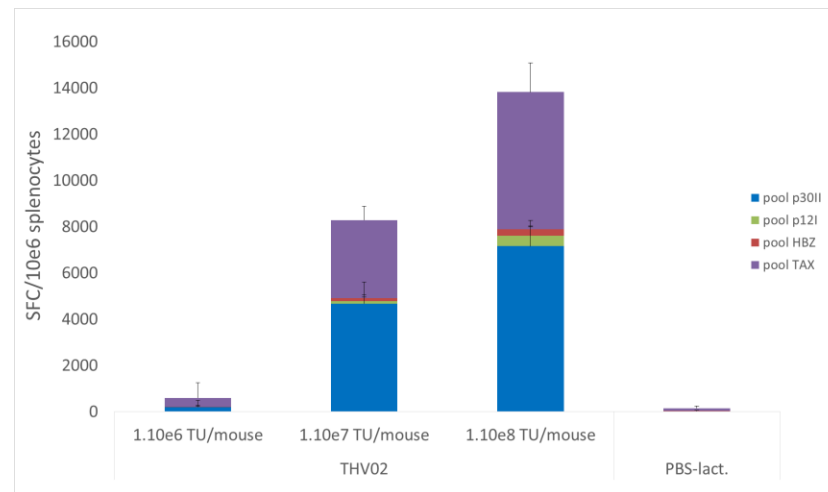


IMMUNOGENICITY IN DIFFERENT ANIMAL SPECIES

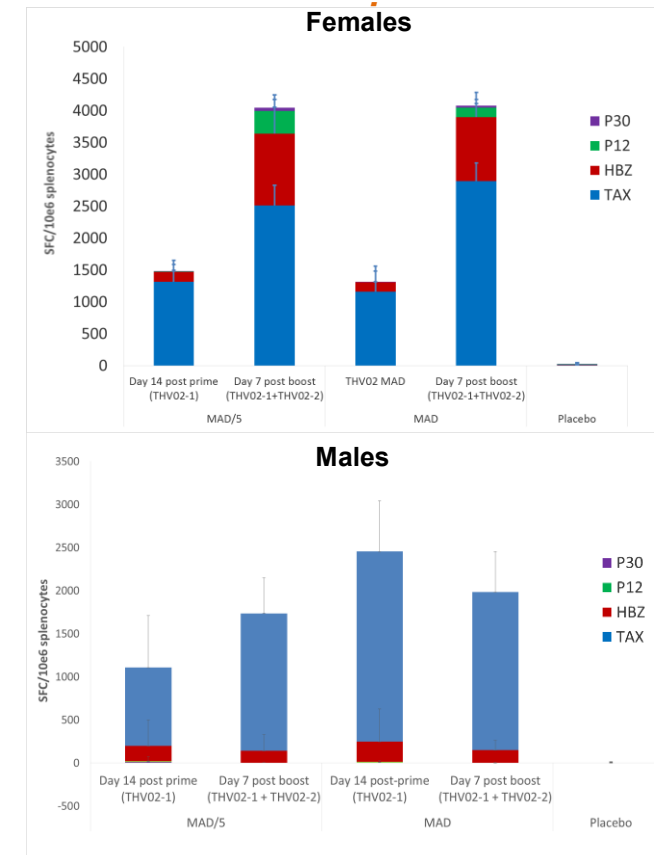


SPECIFIC T-CELL CUMULATIVE RESPONSE (IFN γ SECRETION) IN MEDIAN GROUP VALUE

**Female C57Bl/6j mice, THV02-1 prime*



**Sprague Dawley rats, prime-boost*



=> CCL: difference both in the intensity and the diversity of the immune response according to animal species and sex

• MAD = 2,8.10⁸ TU
• MAD/5 = 0,6.10⁸ TU

Aberrant PD-L1 expression through 3'-UTR disruption in multiple cancers.

Kataoka K1, Shiraishi Y2, Takeda Y3, Sakata S4, Matsumoto M3, Nagano S5, Maeda T5, Nagata Y1, Kitanaka A6, Mizuno S7, Tanaka H2, Chiba K2, Ito S2, Watatani Y1, Kakiuchi N1, Suzuki H1, Yoshizato T1, Yoshida K1, Sanada M8, Itonaga H9, Imaizumi Y10, Totoki Y11, Munakata W12, Nakamura H11, Hama N11, Shide K6, Kubuki Y6, Hidaka T6, Kameda T6, Masuda K5, Minato N13, Kashiwase K14, Izutsu K15, Takaori-Kondo A16, Miyazaki Y10, Takahashi S7, Shibata T11,17, Kawamoto H5, Akatsuka Y18,19, Shimoda K6, Takeuchi K4, Seya T3, Miyano S2, Ogawa S1.

Nature. 2016 Jun 16;534(7607):402-6.

27% Of ATLL ++

8% of DLBCL

2% in gastric carcinoma

Optimal treatment of ATL

Chemo+antibodies (BV, PD1++, KIR3DL2, Tfr)

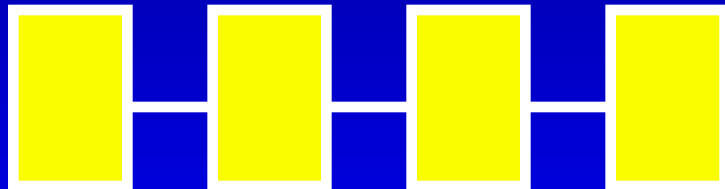
+ antiretroviral

+Epigenetic (EZH2; HDAC)

+Signal transduction (PI3K, JAK1/3i)

+Chemofree (BH3, ITK, Lenalidomide)

CAR-T (BTKi, ibrutinib (Tki, EZH2)

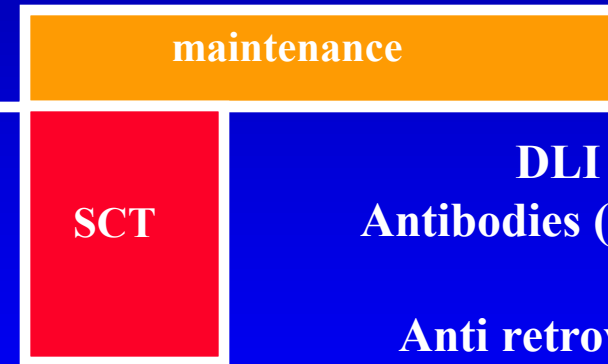


Antibodies (Moga, BV, KIR3DL2, Tfr)

Arsenic

Vaccine

CAR-T?



DLI rev, EZH2i

Antibodies (Moga+JAK2i, BV)

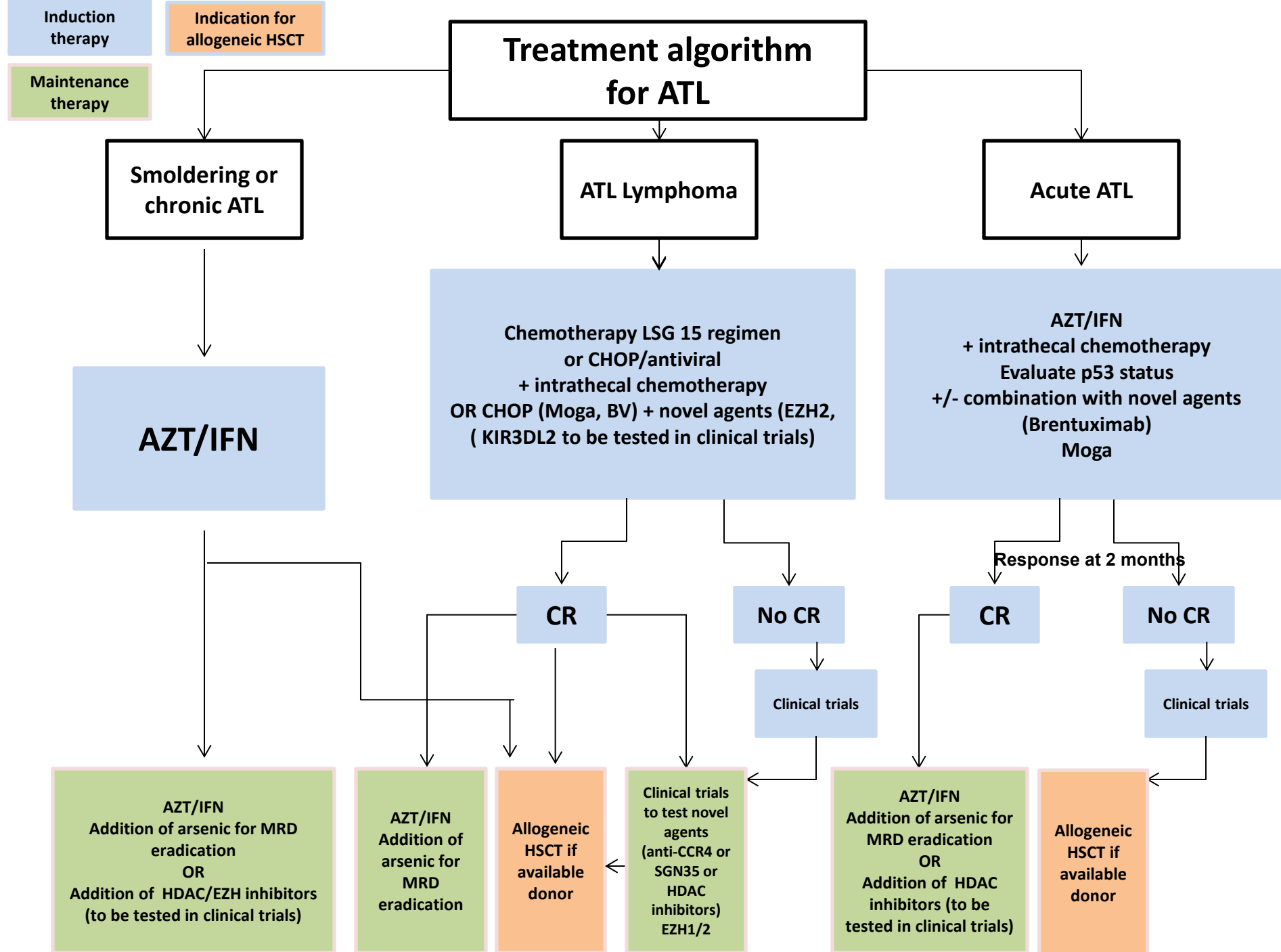
Rev

Anti retroviral and Arsenic

Vaccine

CAR-T?

=> *tumor reduction* => *eradication*



Conclusions and Perspectives

- Physiopathology still unclear : Replication vs no Replication ?
- Targeting the virus ?
- Targeting the tumoral cells and molecular mutations // Personalized medicine vs Universal Treatment ?
- Better understanding of the physiopathology will help to define new strategies
- Immune system (Target ? Understanding the mechanisms of escape ?)
- Treatment of the tumor and virus infection ?

Collaborators

Necker (*A Marçais, M Cheminant, D Ghez, D Sibon, F Suarez*)

American University of Beyrouth (*A Bazarbach*)

Pasteur Institute (*A Gessain*)// Theravectys (*P Charneau*)

ENS Lyon (*R Mahieux*)

Cochin (*Cl Pique*)

Saint Louis (*H de Thé*)

Kansas University (*Ch Nicot*)

Imperial college of London (*C Bangham, G Taylor*)

Mashad University (*R Farid*)