2015…2018.
T-Cell Lymphomas;
We are close to the finalization

Bologna
Royal Hotel Carlton
May 7-9, 2018

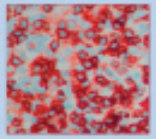
How I treat ATL
in
Standard Treatment in front-line and prognostic index

Kunihiro Tsukasaki, M.D., Ph.D.

Department of Hematology
International Medical Center, Saitama Medical University

2015... 2018
T-Cell Lymphomas:
we are close to the
finalization

Bologna
ROYAL HOTEL CARLTON
May 7-9, 2018



President: Pier Luigi Zinzani
Co-President: Michele Cavo
Honorary President: Sante Tura

Disclosures of Kunihiro Tsukasaki

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Celgene	+				+		
Novartis Pharma					+		
Phyzer					+		
Chugai	+				+		
Kyowa Kirin Hakkou					+		
Glazxo Smith Kleine			+				
Takeda Bio	+						
Symbaio			+				
Ono Pharma			+				
Huya	+		+			+	
Daiichi Sankyo			+			+	

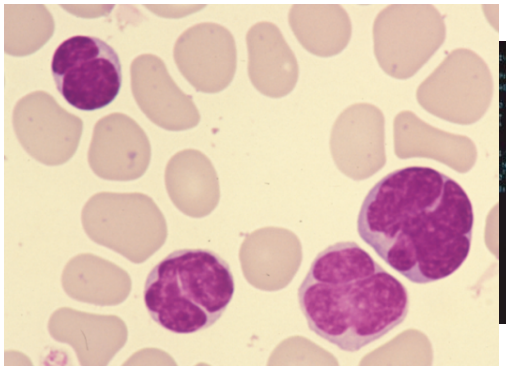
Adult T-cell leukemia-lymphoma（ATL）

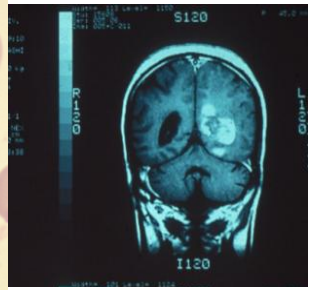
・Mature T-cell malignancy of Th2/Treg origin associated with HTLV-1

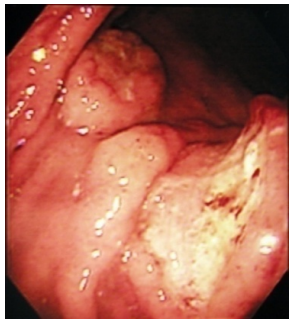
・Several tens millions of HTLV-1 carriers in the world, endemic in south-west coast of Japan, mid-and south-America and Africa

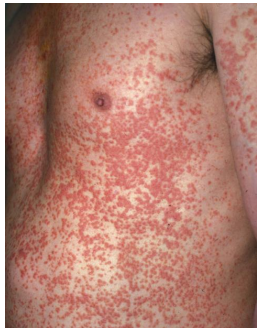
・About 5% of HTLV-1 carriers develop ATL during their life time

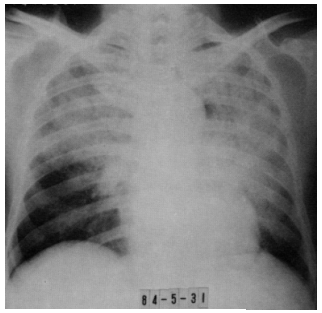
・Clinical feature is diverse and treatment strategy is based on subtype classification

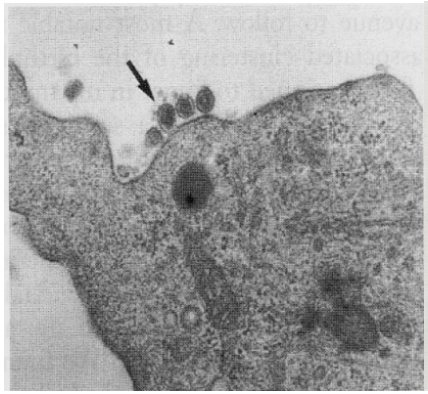


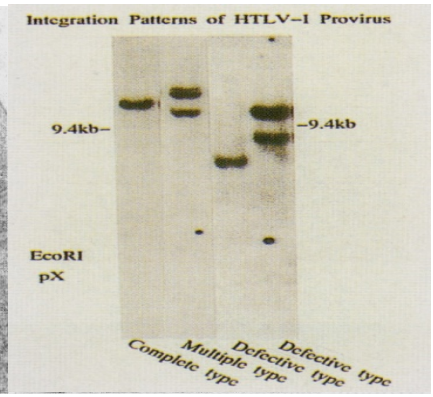


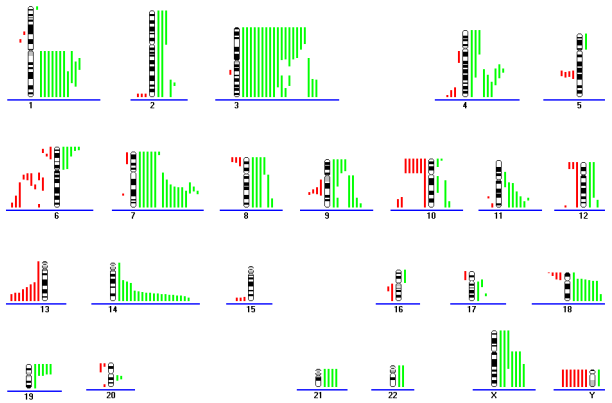






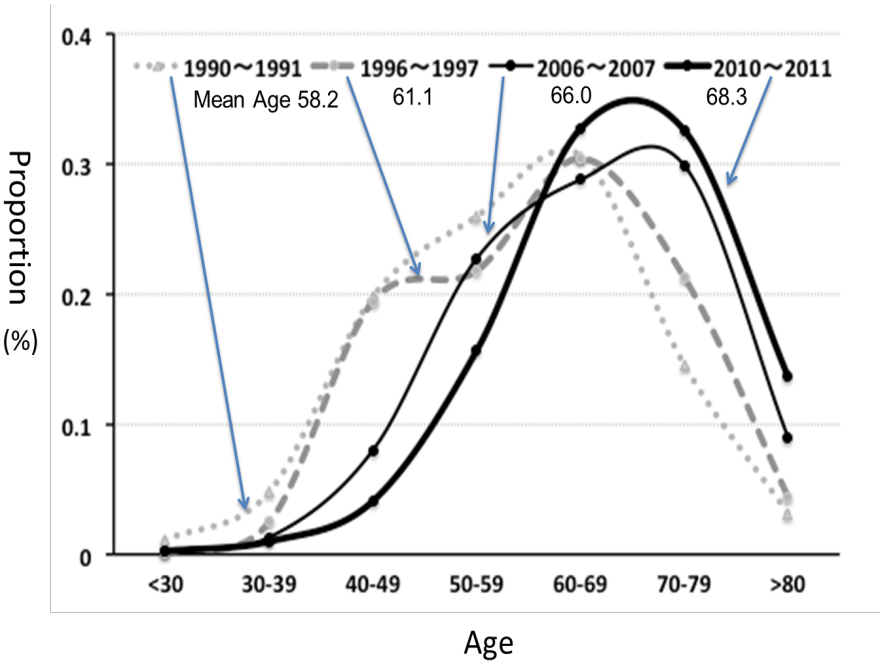


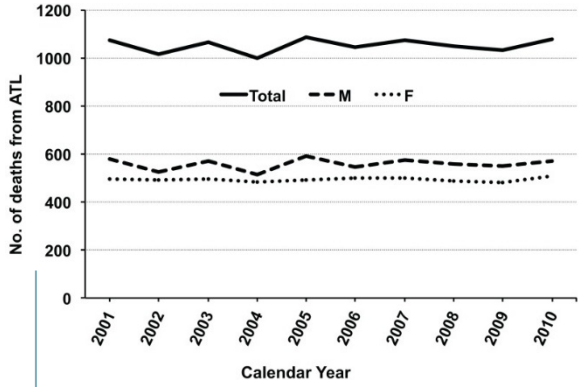




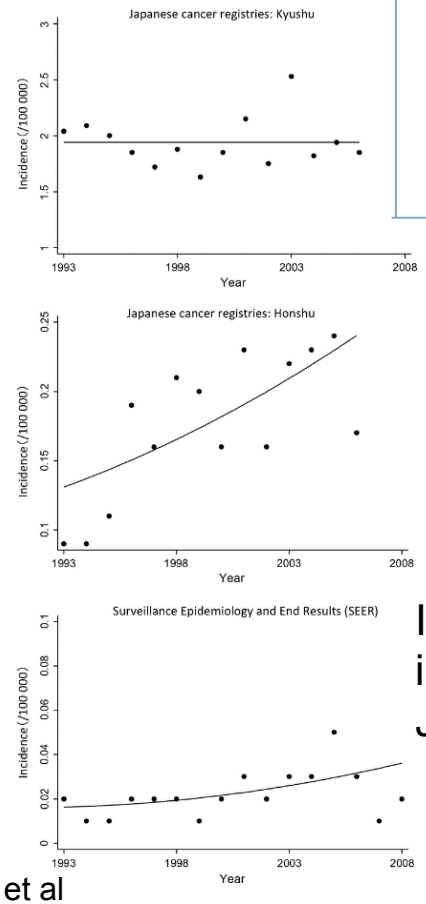
Epidemiology of ATL in Japan and USA

Rapid aging of patients with ATL;
Consecutive nation-wide surveys in Japan





No. of deaths from ATL 2001–2010 in Japan
from vital statistics in the Portal Site of Official Statistics of Japan (e-Stat; accessed April 8, 2012).



Areas	APC (95%CI)
Kyusyu	0.0 (−1.6, 1.7)
Honsyu	4.6 (1.1, 8.2)
USA	6.2 (1.5, 11.1)

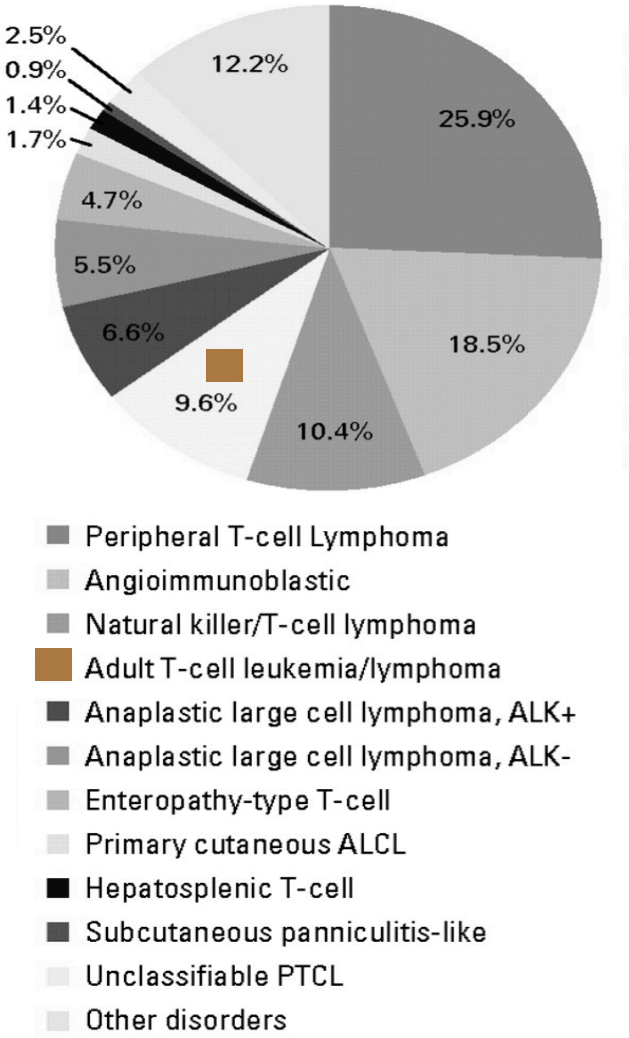
APC; annual percent change

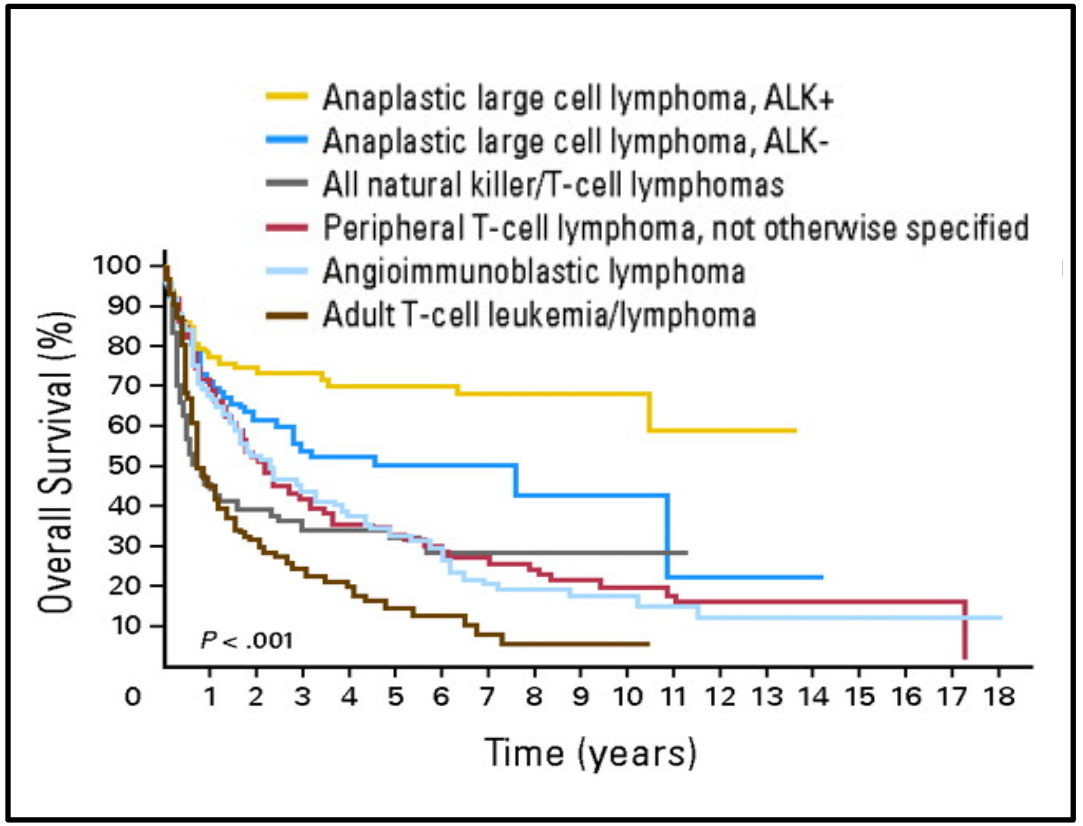
Increase in incidence of ATL in non-endemic area of Japan and USA

Cancer Sci. 2017
Nosaka K, Tsukasaki K, et al

Cancer Sci. 2012
Chihara D, et al

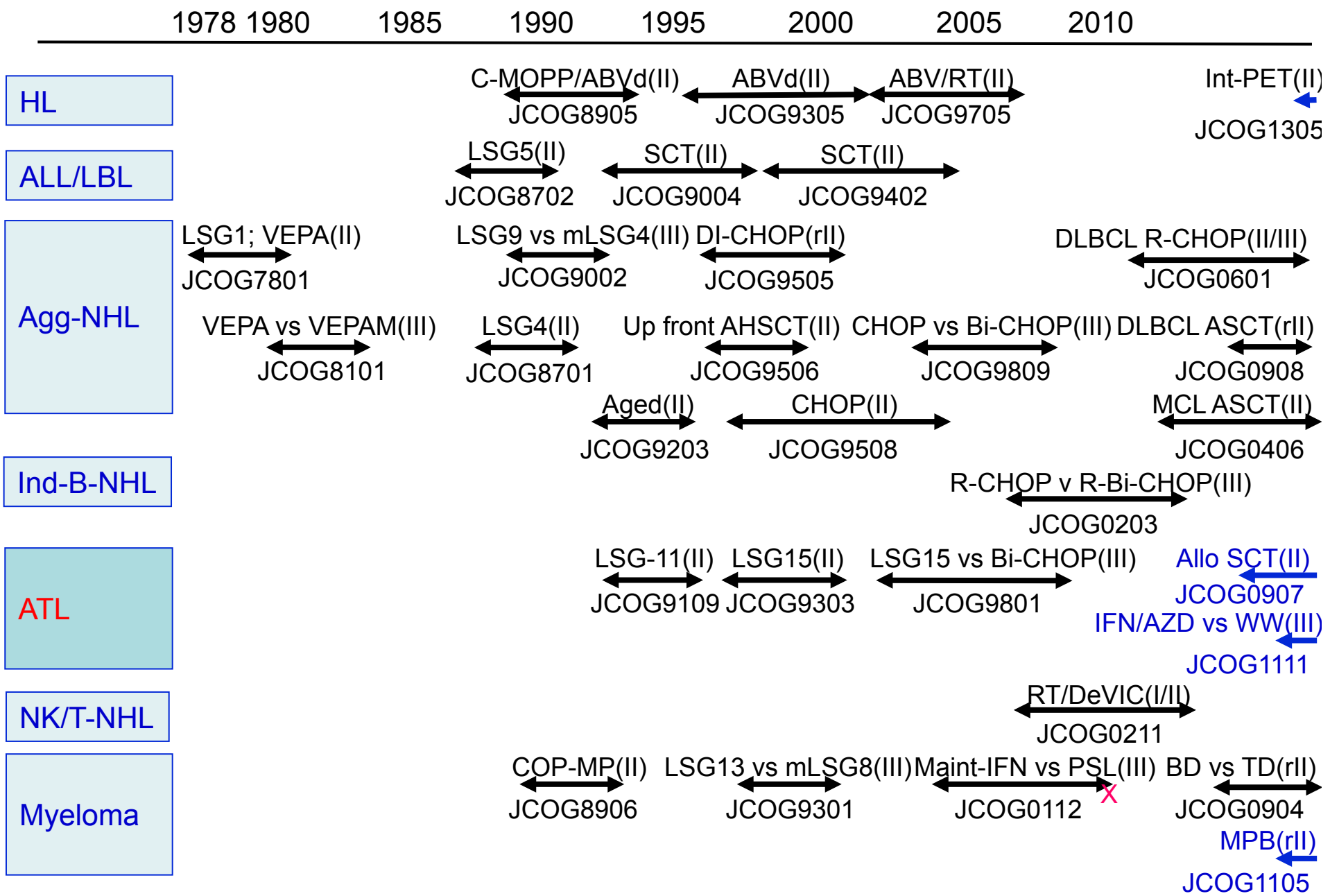
International peripheral T-cell and NK/T-cell lymphoma study: pathology findings and clinical outcomes on 1314 cases.





International T-Cell Lymphoma Project: J Clin Oncol、2008

31 Consecutive studies by JCOG-LSG



Comparison of CR rates by disease and chemotherapy in initial LSG trials for aggressive NHL

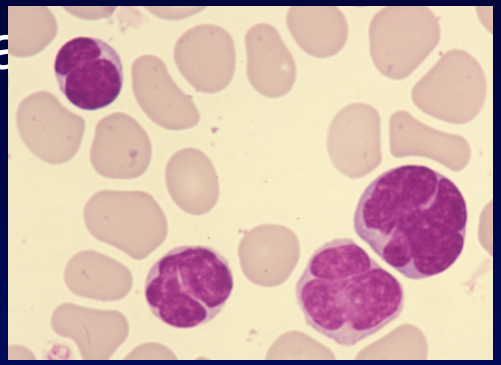
	B-lymphoma	PNTL	ATL	Total
7801(VEPA)	65/101 (64%)	17/30 (57%)	7/42 (17%)	95/182 (52%)
8101(VEPAM)	33/40 (83%)	5/9 (56%)	11/30 (37%)	51/82 (62%)
8701(LSG4)	123/151 (82%)	28/42 (67%)	18/43 (42%)	193/267 (72%)

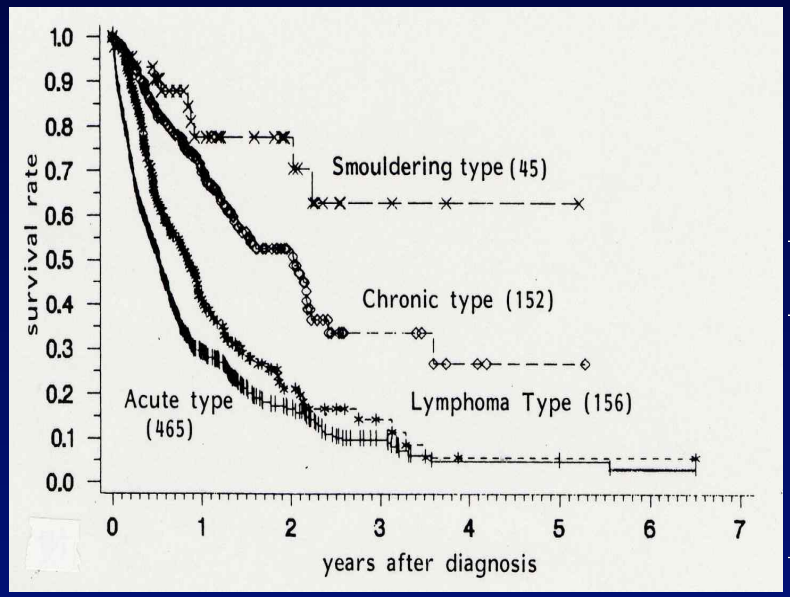
ATL; adult T-cell leukemia-lymphoma
PNTL; peripheral non-ATL T-lymphoma

Shimoyama et al. JCO 5: 128 and JCO 6:1088,1988

Nationwide survey for ATL by JCOG-LSG: 1984-1987 (n=854)

- Multi-variate analysis revealed 5 independent prognostic factors (LSG, Leuk Res, 1991) ;
  - PS, Age>60, LDH, Ca and No. of Total Involved Lesions
- Establishment of ATL subtypes based on natural history, clinical features and prognostic fa

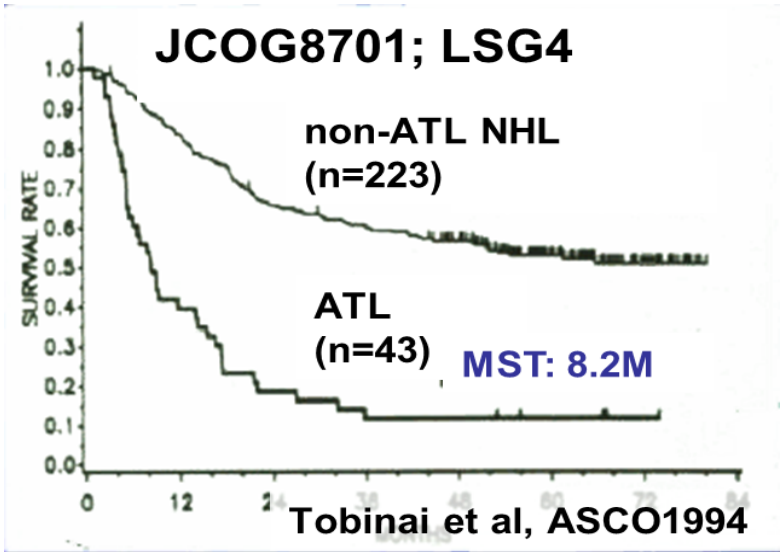


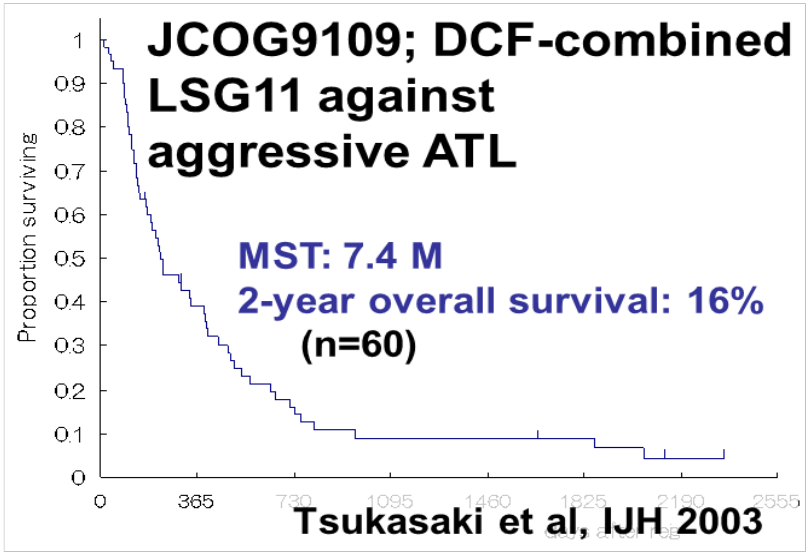


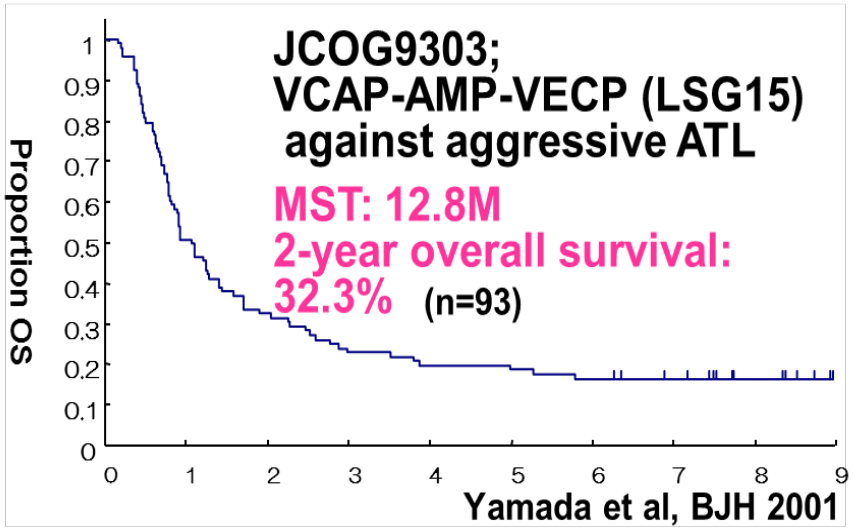
Clinical subtype:	Smoldering/Chronic	Acute/Lymphoma
Organ involvement	No / Minimum (Skin etc)	Yes
LDH level	Normal or raised =< x2	Raised > x 2
Calcium level	Normal	Raised
Median survival time	> 24 months	6-10 months

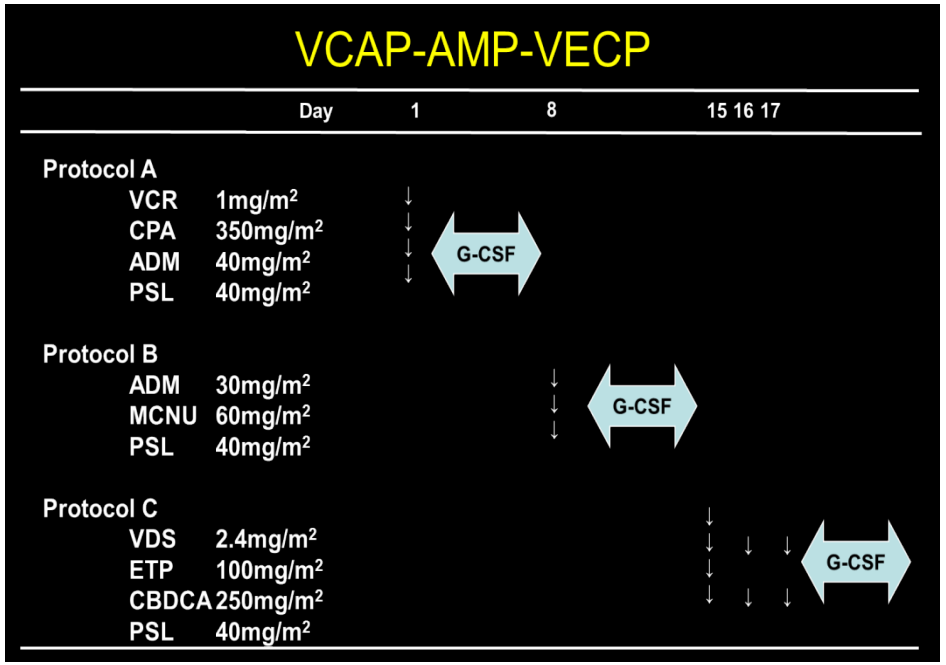
Shimoyama M, et al. B J Haematol, 1991

Consecutive Trials for ATL by JCOG-LSG



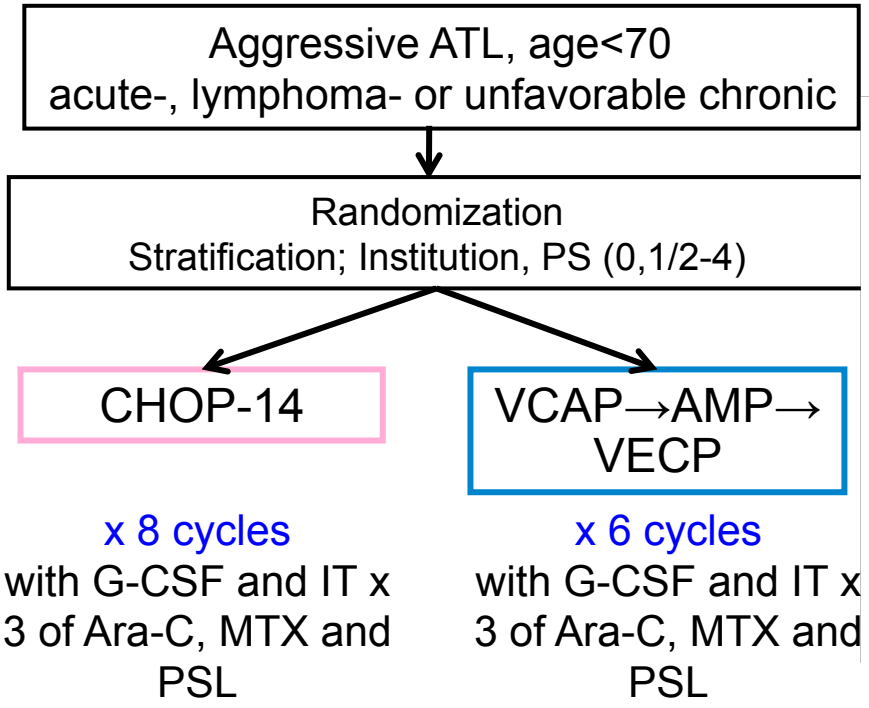


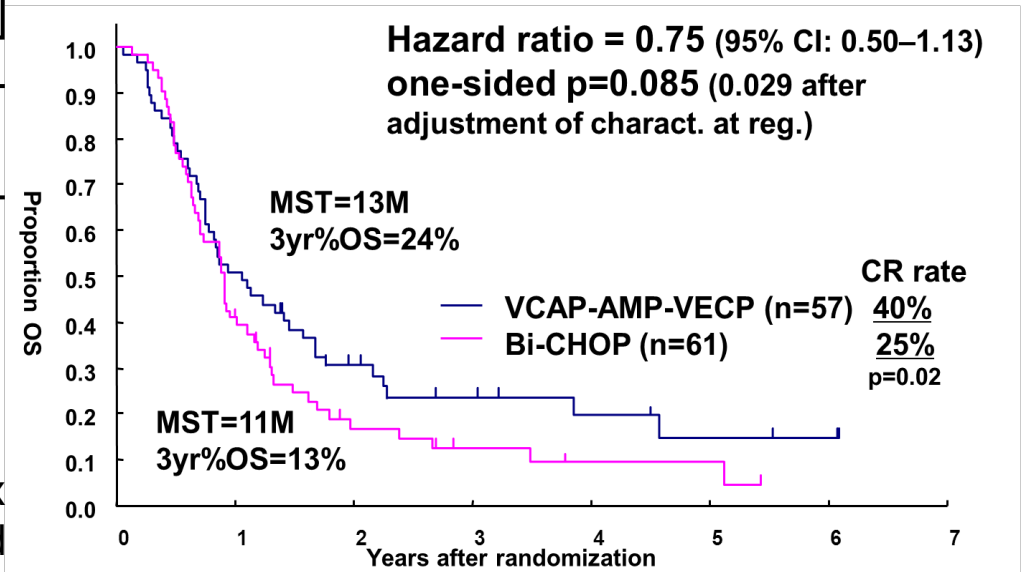




P-Ⅲ study of VCAP-AMP-VECP vs. CHOP-14

in aggressive ATL:JCOG9801





VCAP-AMP-VECP is a more effective regimen at the expense of higher toxicities, providing the basis for future investigations in the treatment of ATL

Tsukasaki K, et al. J Clin Oncol, 2007

JCOG0902A: Characterization of Long-Term Survivors and a Predictive Model for Aggressive ATL

Fukushima et al. 52nd ASH Annual Meeting, 2011.

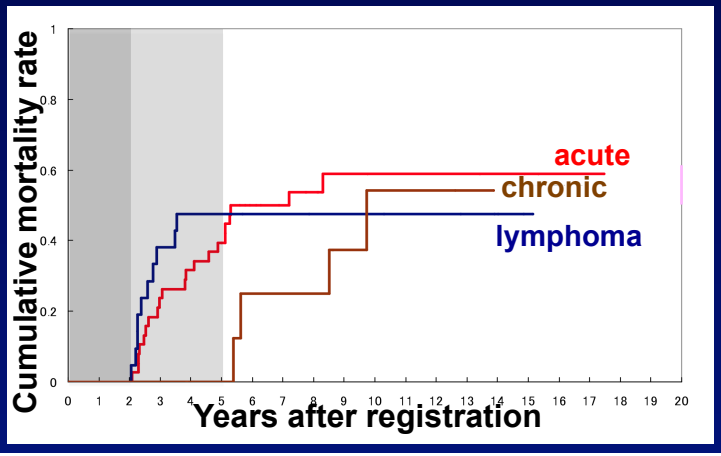
Objective

1. Characterize long-term survivors
2. Develop a prognostic model (JCOG-PI)
   stepwise Cox regression analysis and external validation

Patients

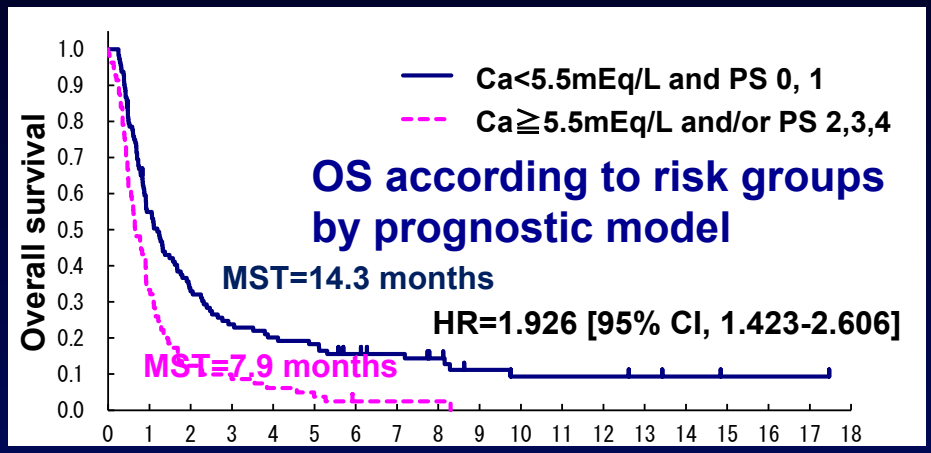
	all	surivors over 5-y	surivors over 2-y	test sample
JCOG9109	62	8	5	40
JCOG9303	96	30	17	57
JCOG9801	118	29	15	96
Total	276	37	67	193

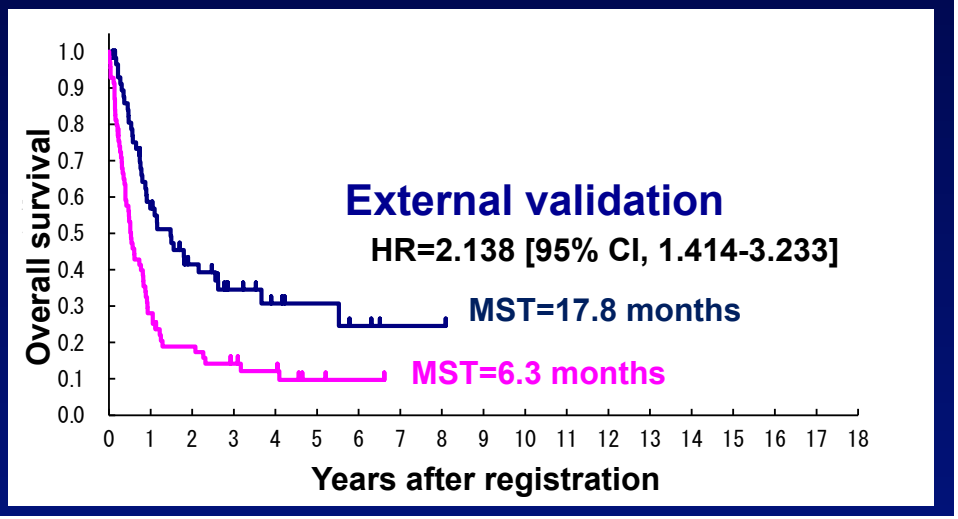
Validation sample: 127



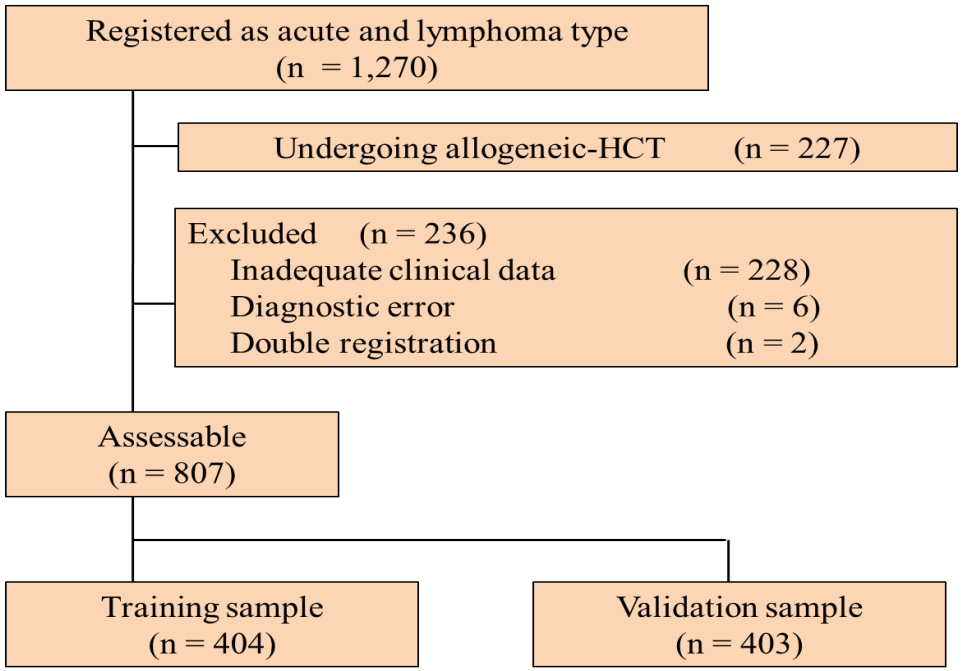
stepwise Cox regression

Prognostic factor	HR (95%CI)	P value
Ca≧5.5mEq/L (vs <5.5mEq/L)	1.688 (1.156-2.466)	0.007
PS: 2, 3, 4 (vs 0, 1)	1.493 (1.073-2.078)	0.018



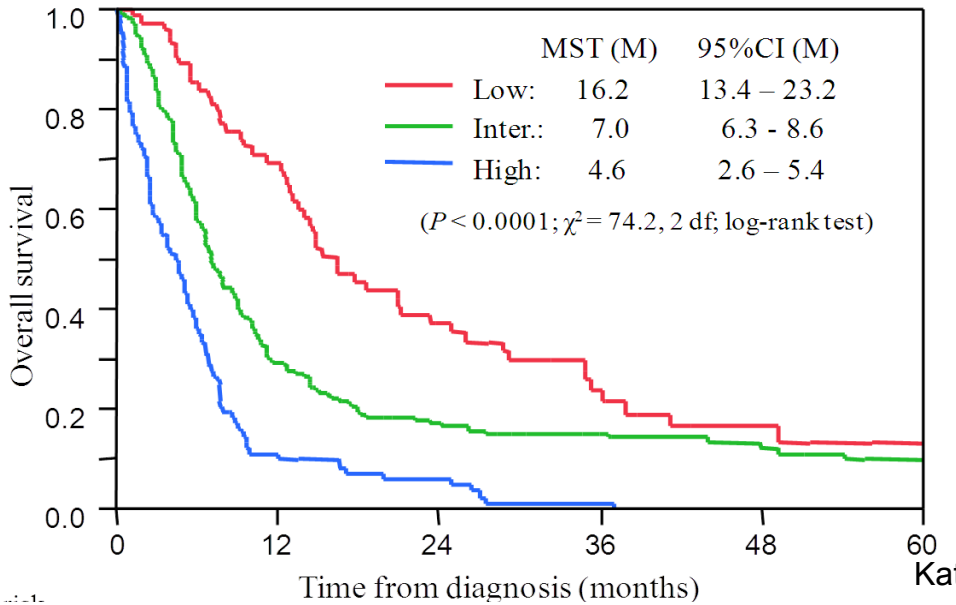


ATL-PI for acute-/lymphoma-type ATL from Japan



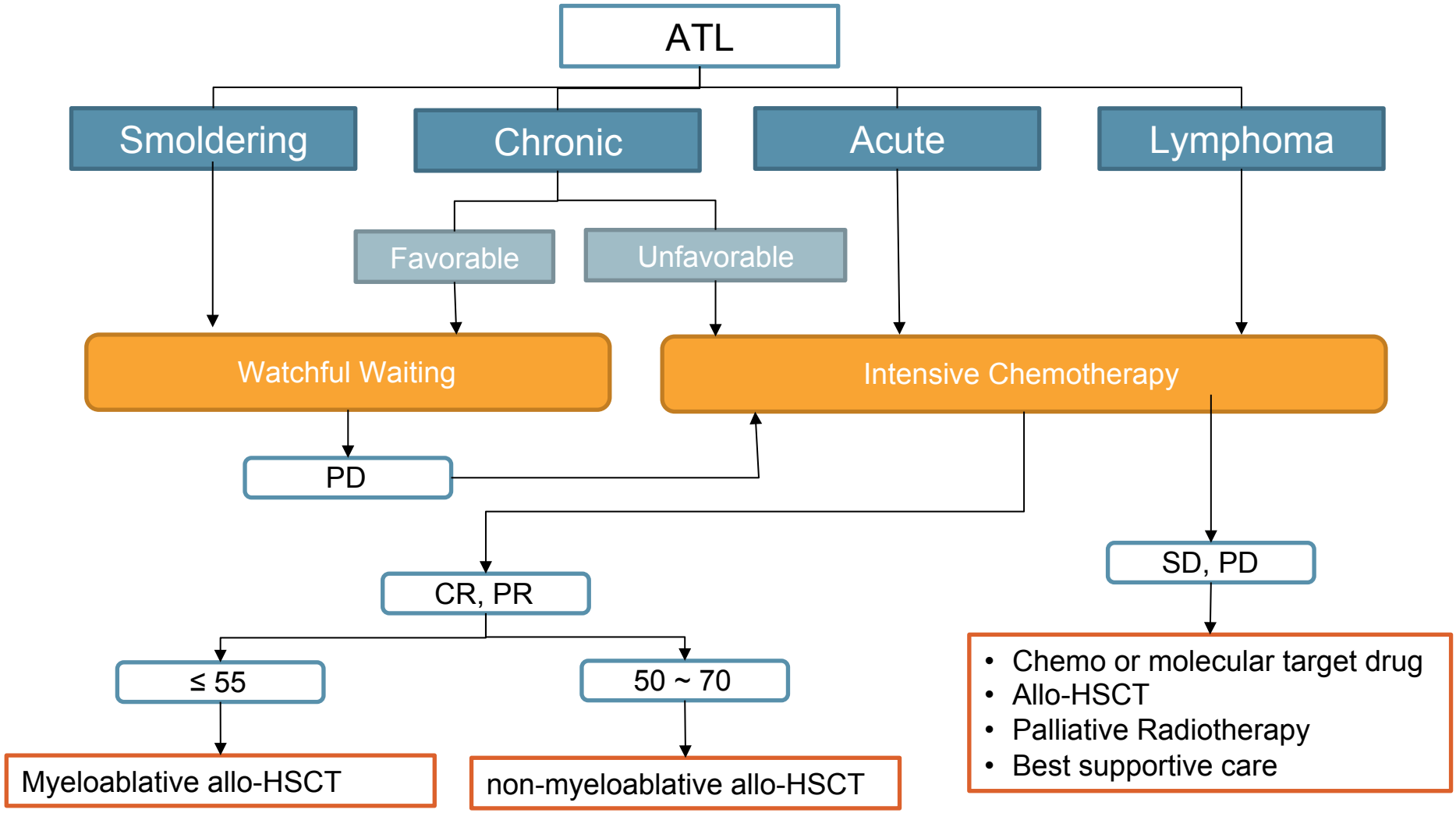
		Score
Stage	III or IV (90%)	2
Age (year)	> 70	1
Serum Albumin (g/dl)	< 3.5	1
ECOG PS	2~4 (51%)	1
sIL-2R (U/ml)	>20,000	1

Sum of the scores
0・1・2 ⇒ Low risk
3・4 ⇒ Intermediate risk
5・6 ⇒ High risk



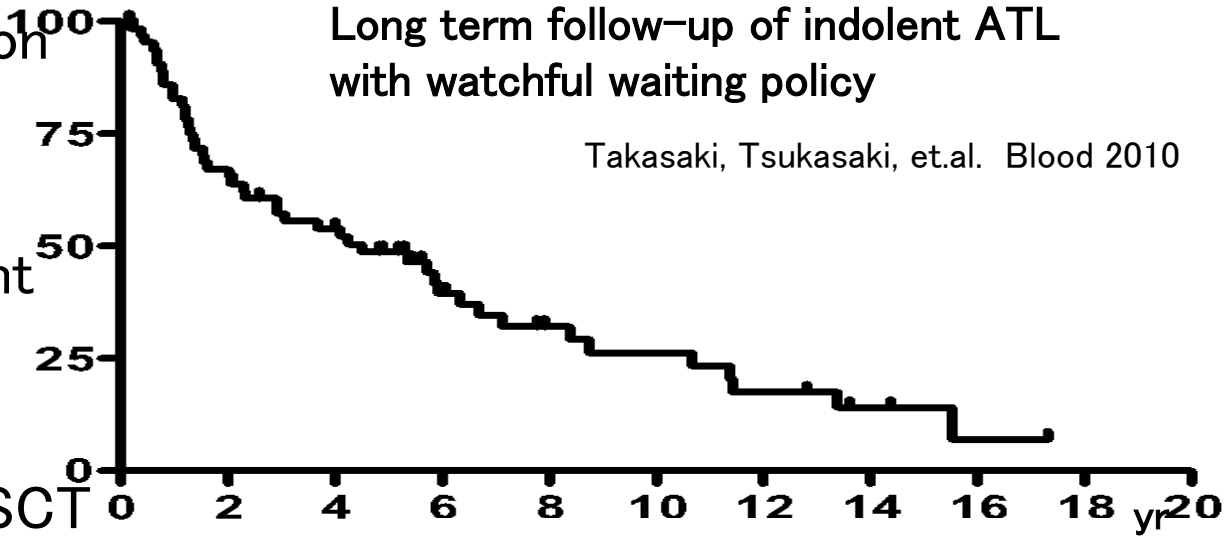
Katsuya H, Tsukasaki K, et al, JCO 2012

Overall Schema for Treatment of ATL: Guideline 2013 by Japanese Society of Hematology



Prognosis of ATL in relation to clinical subtypes and treatment modalities

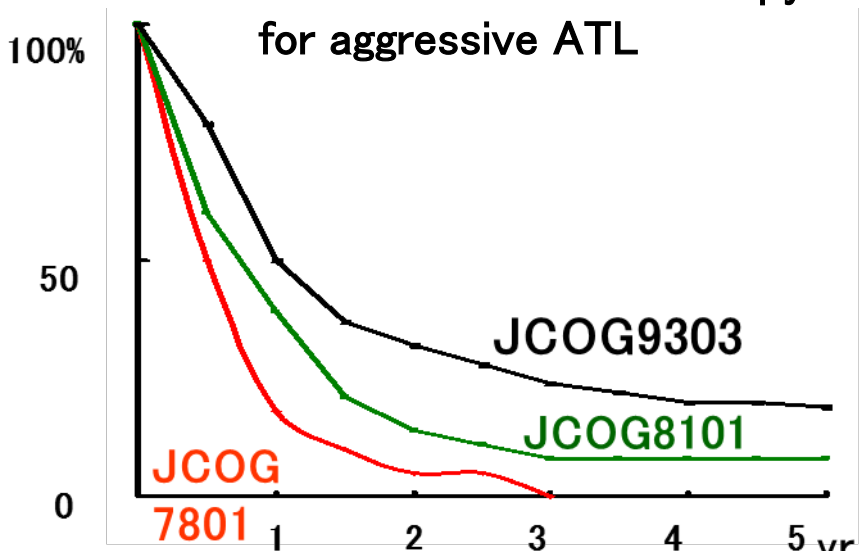
- Poor prognosis of indolent ATL after long follow-up
- Improved prognosis of aggressive ATL after both chemotherapy and allo-HSCT



Long term follow-up of indolent ATL with watchful waiting policy

Takasaki, Tsukasaki, et.al. Blood 2010

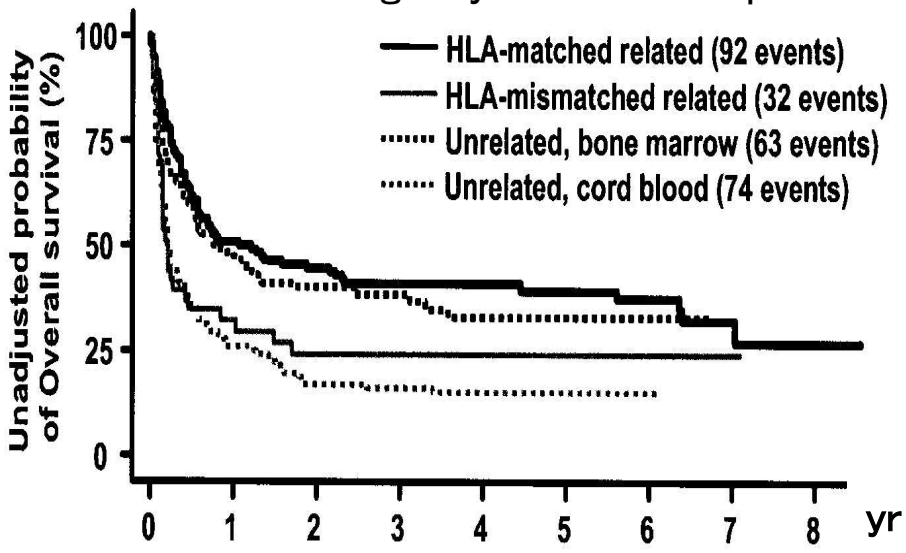
Consecutive trials of chemotherapy for aggressive ATL



Shimoyama, et al. 2006,

Allo-HSCT for aggressive ATL

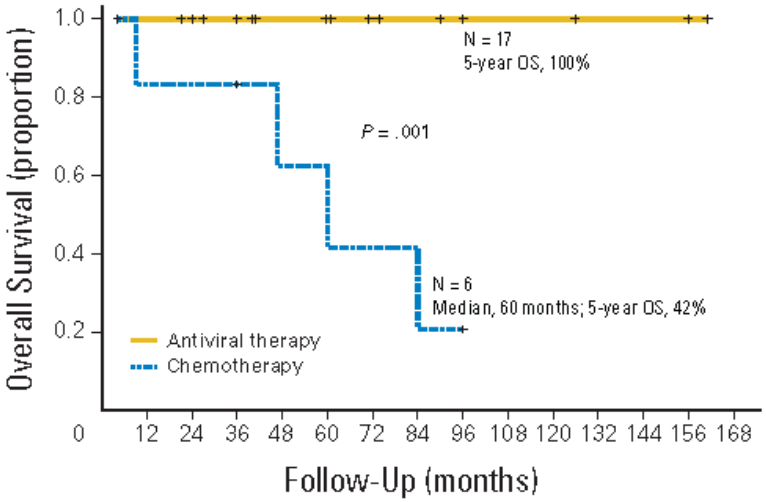
Registry data of 386 pts



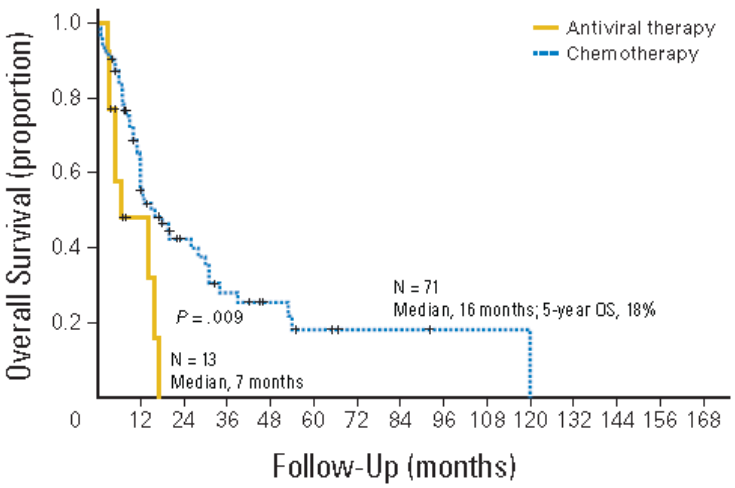
Hishizawa M et.al. Blood 2010

Interferon/Zidobudine for ATL
－Retrospective survey－

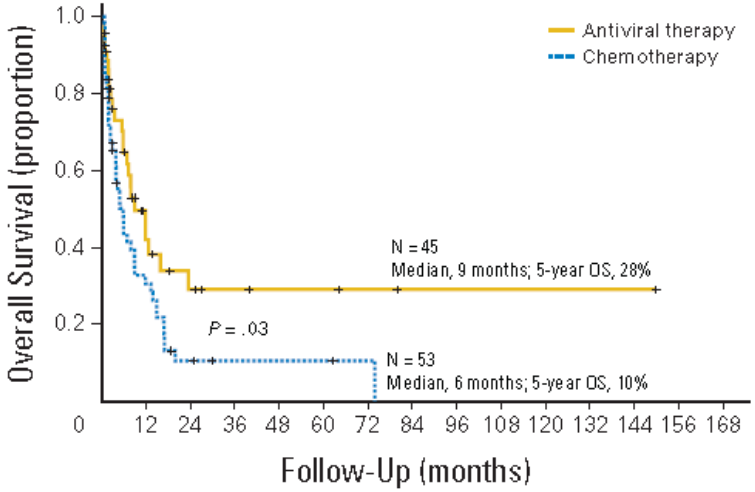
A Chronic and smoldering



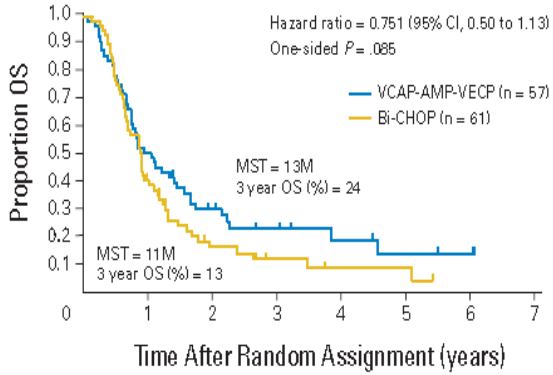
B Lymphoma



C Acute



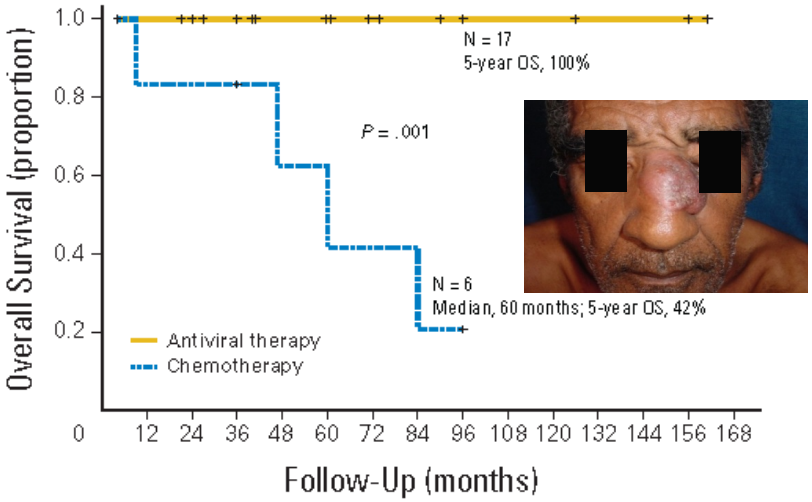
JCOG9801



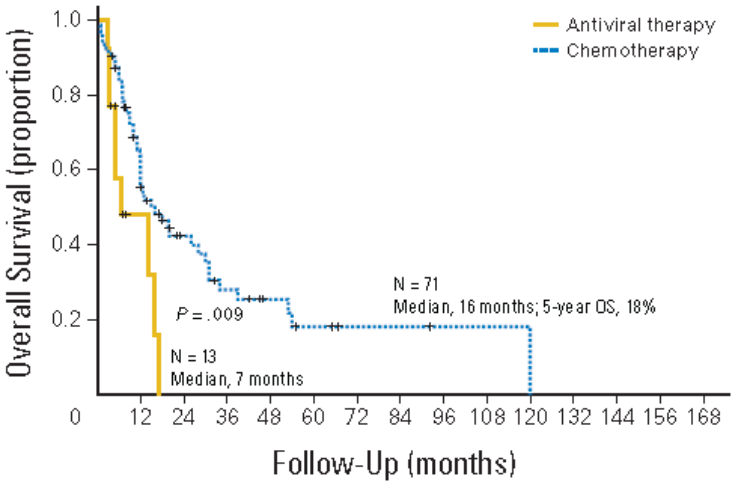
Bazarbachi, A, et al, J Clin Oncol 2010

Interferon/Zidobudine for ATL
—Retrospective survey—

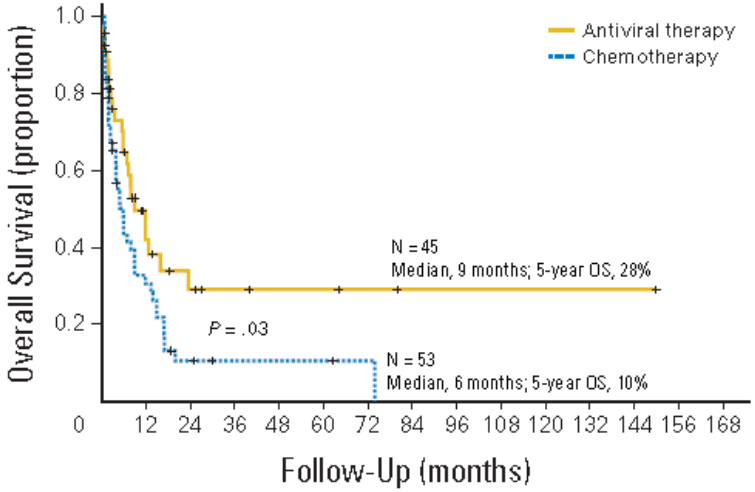
A Chronic and smoldering



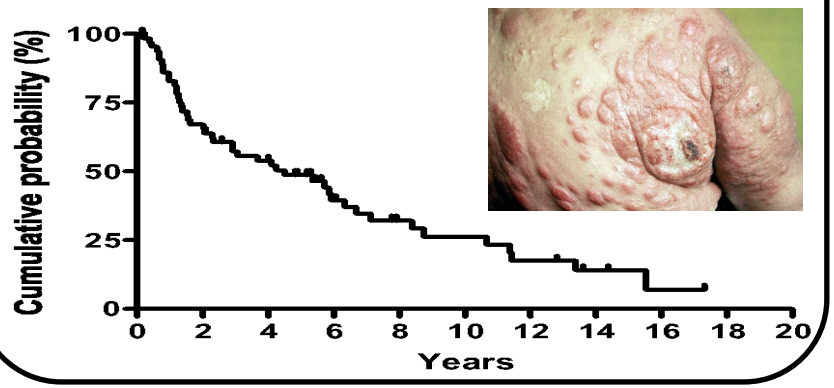
B Lymphoma



C Acute



indolent ATL with watchful waiting



Bazarbachi, A, et al, J Clin Oncol 2010

Recommended strategy for the treatment of ATL

Smoldering- or favorable chronic-type ATL

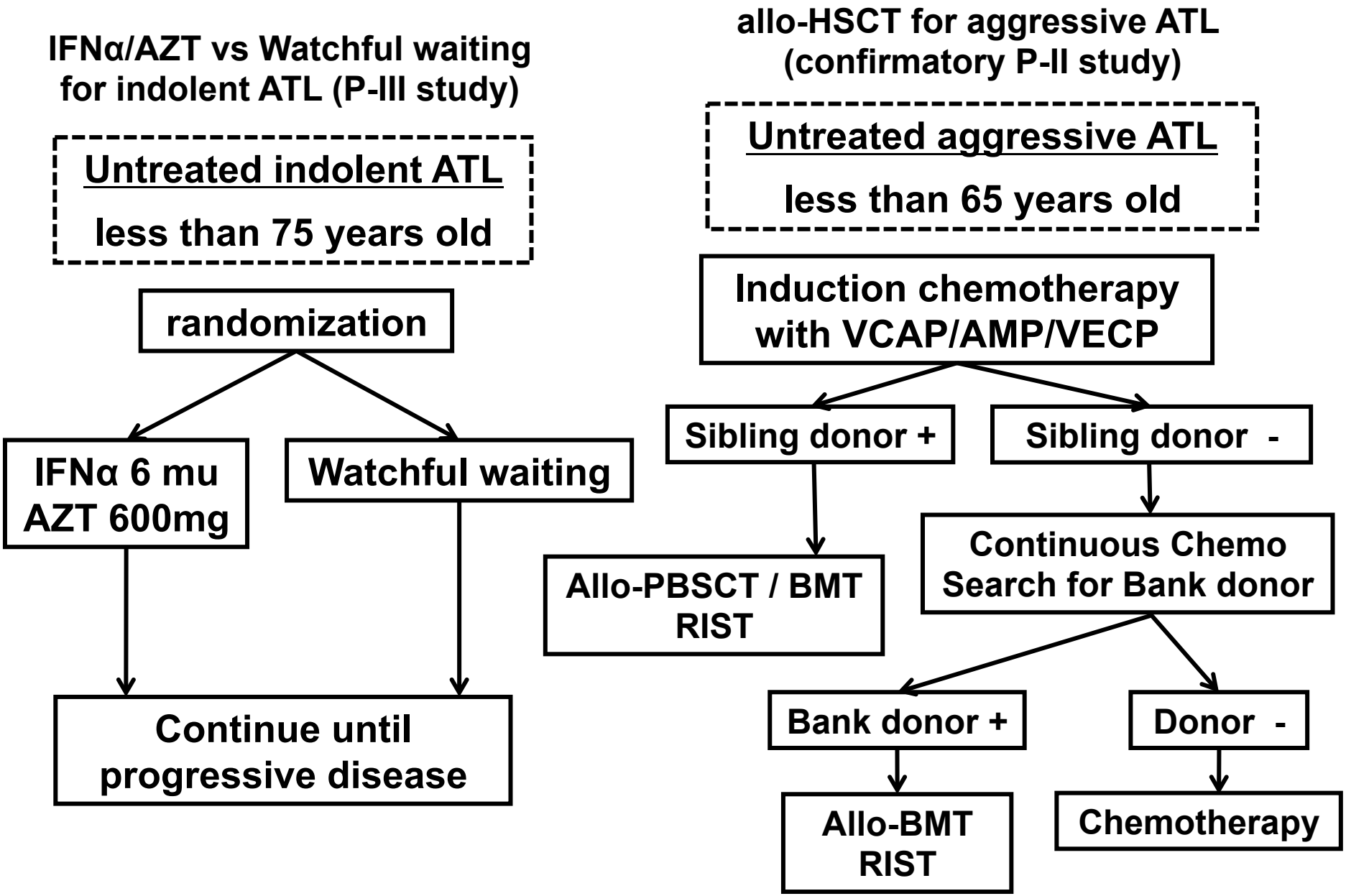
- Symptomatic patients (skin lesions, opportunistic infections, etc): Consider AZT/IFN or Watch and Wait
- Asymptomatic patients: Consider Watch and Wait

Unfavorable chronic- or acute-type ATL

- If outside clinical trials, check prognostic factors (including clinical and molecular factors if possible):
  - Good prognostic factors: consider chemotherapy (VCAP-AMP-VECP evaluated by a phase III trial against CHOP-14) or AZT/IFN (evaluated by a meta-analysis on retrospective studies)
  - Poor prognostic factors: consider chemotherapy followed by conventional or reduced intensity allo-HSCT (evaluated by retrospective and prospective Japanese studies, respectively).
  - Poor response to initial therapy: Consider conventional or reduced intensity allo-HSCT

International ATL Consensus Report;
Tsukasaki, Ermine, Bazarbacchi, et al; J Clin Oncol, 2009

Ongoing ATL trials by JCOG-LSG



New agents are approved and under clinical development in ATL

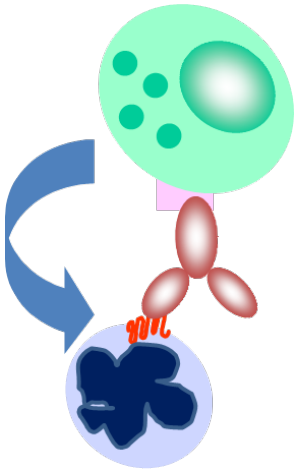
Compound	MOA	Target	Phase
Mogamulizmab	Anti-CCR4 Ab	CCR4+ R ATL	Approved
Lenalidomide	Immune modulatory	R/R ATL	Approved
DS3201	EZH 1and 2 inhibitor	R/R ATL	I
Nivolumab	Anti-PD 1	R/R ATL	II
Abacavir	Nucleoside Reverse Transcriptase Inhibitor	R/R ATL	II
NY-ESO-1 Vaccine	T-cell receptor gene therapy	ATL with NY-ESO positive	Ia/Ib
Chydamide	Histone deacetylase inhibitor (HDACI)	R/R ATL	II
Tax-DC vaccine	Modulation of Tax specific CTLs	ATL	Ia/Ib

Mogamulizumab, a defucosylated anti-CCR4 Ab in ATL

ADCC

Antibody-dependent cellular cytotoxicity

- One of the most important functions of the therapeutic antibodies
- Development of a first-in-class zero-fucose humanized antibody with high ADCC activity targeting CCR4



CCR4

CC chemokine receptor 4

- receptor for TARC & MDC
- G-protein coupled receptor
- Expression in cancer: some of the T cell lymphoma /leukemia
- Expression in normal tissues: some of the peripheral T-lymphocytes (Th2/Treg cells)

P-1 study of Mogamulizumab in relapsed PTCL/ATL

- MTD was not reached until 1mg/kg in 16 pts.
- RR was 31% including 2 CRs among 13 ATL patients.

→ Recommended phase II dose: 1.0 mg/kg

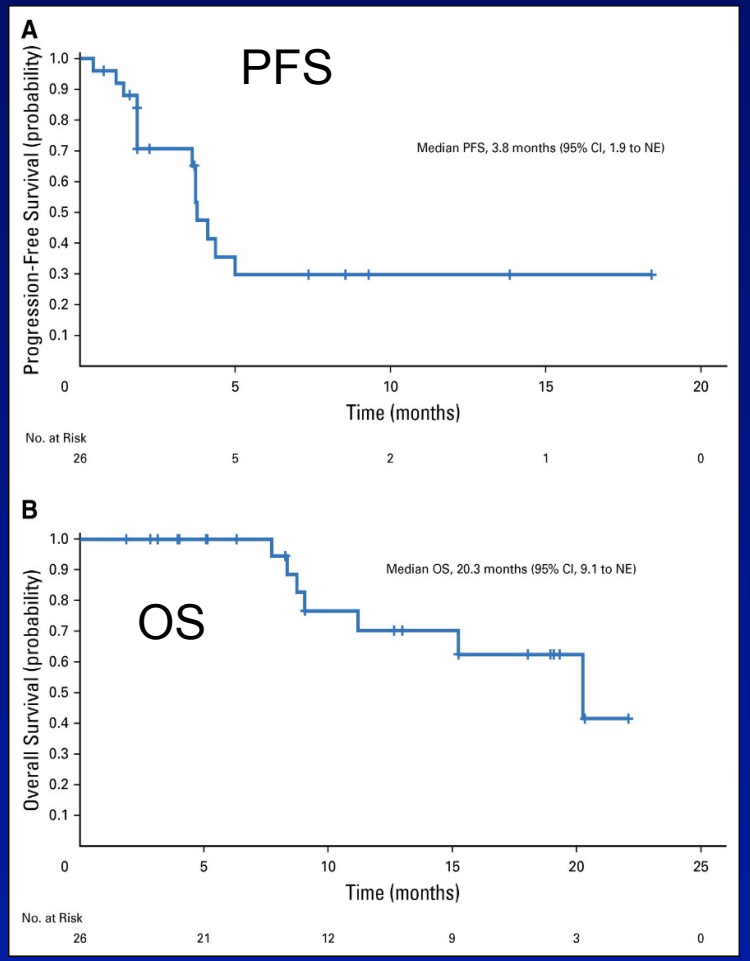
P-2 study of Mogamulizumab in relapsed aggressive ATL

		Best response					Response rate		
Disease site	n	CR	PR	SD	PD	NE	≥ PR	(%)	[95% CI]
Blood	13	13	0	0	0	0	13	(100 %)	-
Skin	8	3	2	0	2	1	5	(63 %)	[25-92)
Nodal & extranodal	12	3	0	4	5	0	3	(25 %)	[6-57]
Overall**	26	8	5	2	11	0	13	(50 %)	[30-70]

JCO 20

PII Study of Lenalidomide in Pts With R/R ATL
Lenalidomide 25 mg/day given continuously

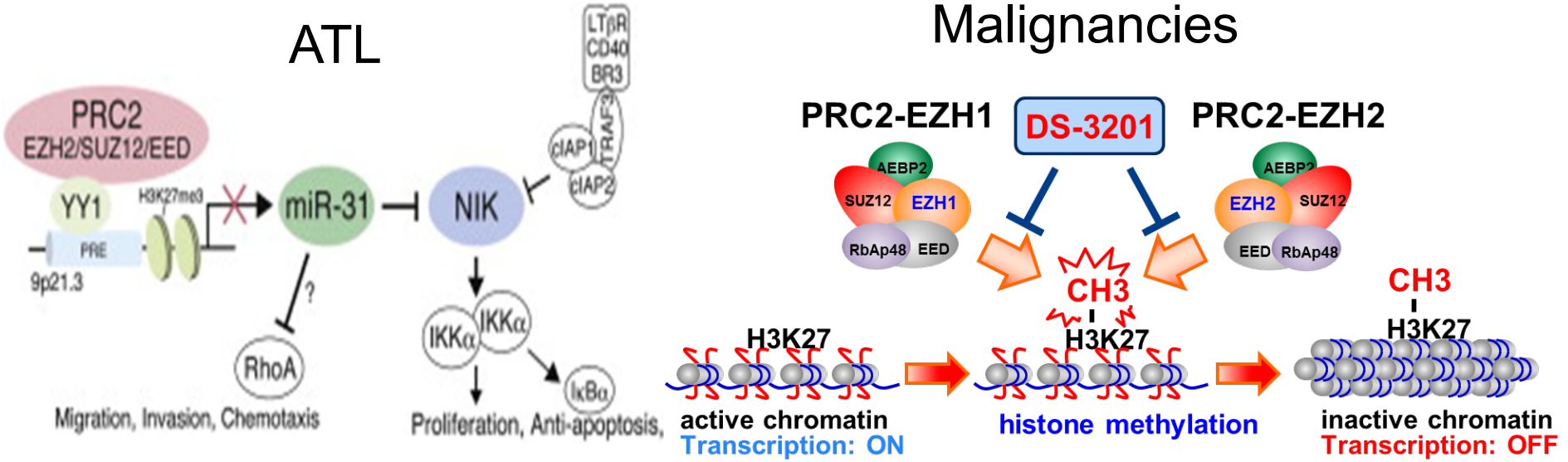
Population, n (%)	n	ORR	CR/ CRu	PR	SD	PD
All patients	26	11 (42)	5 (19)	6 (23)	8 (31)	7 (27)
By type						
Acute	15	5 (33)	3 (20)	2 (13)	6 (40)	4 (27)
Lymphoma	7	4 (57)	2 (29)	2 (29)	0	3 (43)
Unfavorable chronic	4	2 (50)	0	2 (50)	2 (50)	0
By prior mogamulizumab						
Yes	11	2 (18)	1 (9)	1 (9)	6 (55)	3 (27)
No	15	9 (60)	4 (27)	5 (33)	2 (13)	4 (27)
By lesion						
Target lesion	16*	5 (31)	5 (31)	0	8 (50)	2 (13)
PGA	8	6 (75)	4 (50)†	2 (25)	2 (25)	0
Peripheral blood	10	6 (60)	4 (40)	2 (20)	2 (20)	2 (20)



- Responses were observed in all lesion types

Ishida T, Tsukasaki K, et al. JCO 2016

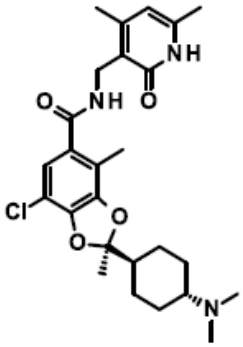
EZH1/2 Dual Inhibitor



- Polycomb-mediated loss of miR-31 activates NIK-dependent NF-κB pathway in ATL and other cancers.
- EZH1 and EZH2 are methyltransferases which specifically methylate histone H3 lysine 27 by forming a multi-protein complex termed polycomb repressive complex 2 (PRC2). Both PRC2-EZH1 and PRC2-EZH2 can create tri-methylated H3K27, which is important for suppression of tumor suppressor genes or cell differentiation genes.
- DS-3201b is a dual inhibitor of EZH 1 and EZH2, an oral agent, that has demonstrated anti-tumor activity against ATL in preclinical studies.

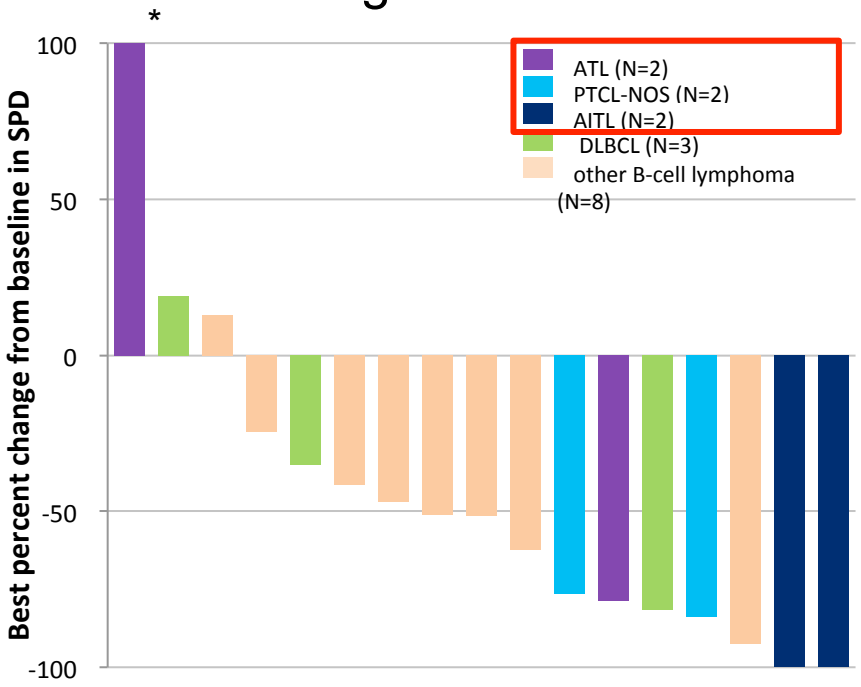
FIH Study of the EZH1/2 Dual Inhibitor, DS-3201b

Best Response	B-cell lymphoma (n=11)	T-cell lymphoma (n=6)	All (n=17)
CR, n (%)	0 (0)	1 (16.7)	1 (5.9)
PR, n (%)	5 (45.5)	4 (66.7)	9 (52.9)
SD, n (%)	4 (36.4)	0 (0)	4 (23.5)
PD, n (%)	2 (18.2)	1 (16.7)	3 (17.6)

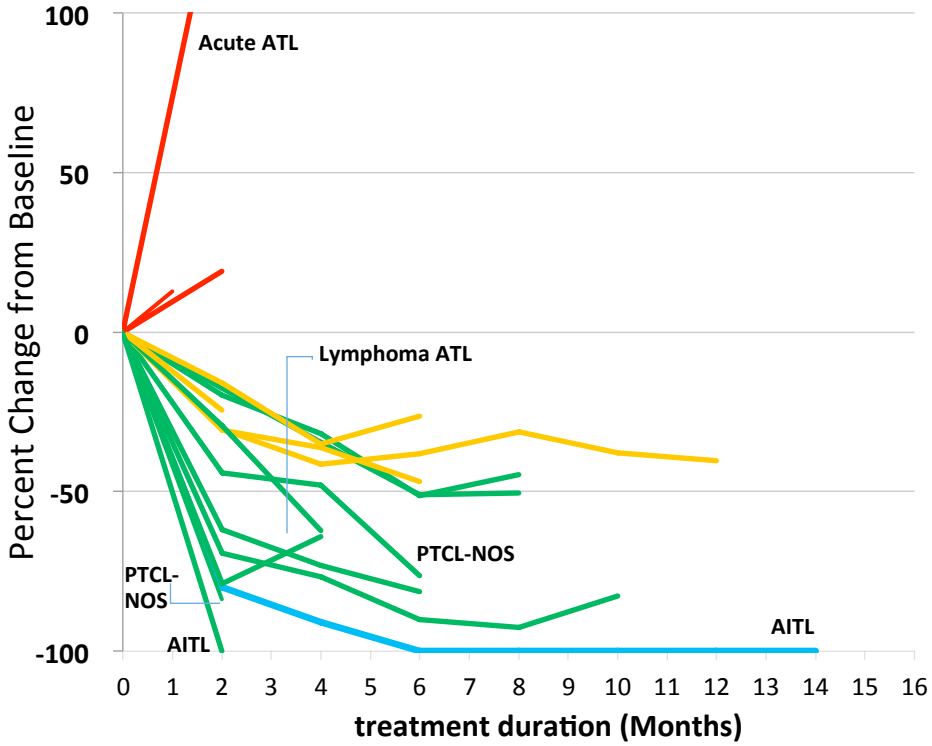


DS-3201

Maximum Percentage Improvement for Target Lesion SPD



Percentage Change in Tumor Size Over Time



Maruyama D, Tsukasaki K, et al. ASH 2017. Abstract 4070

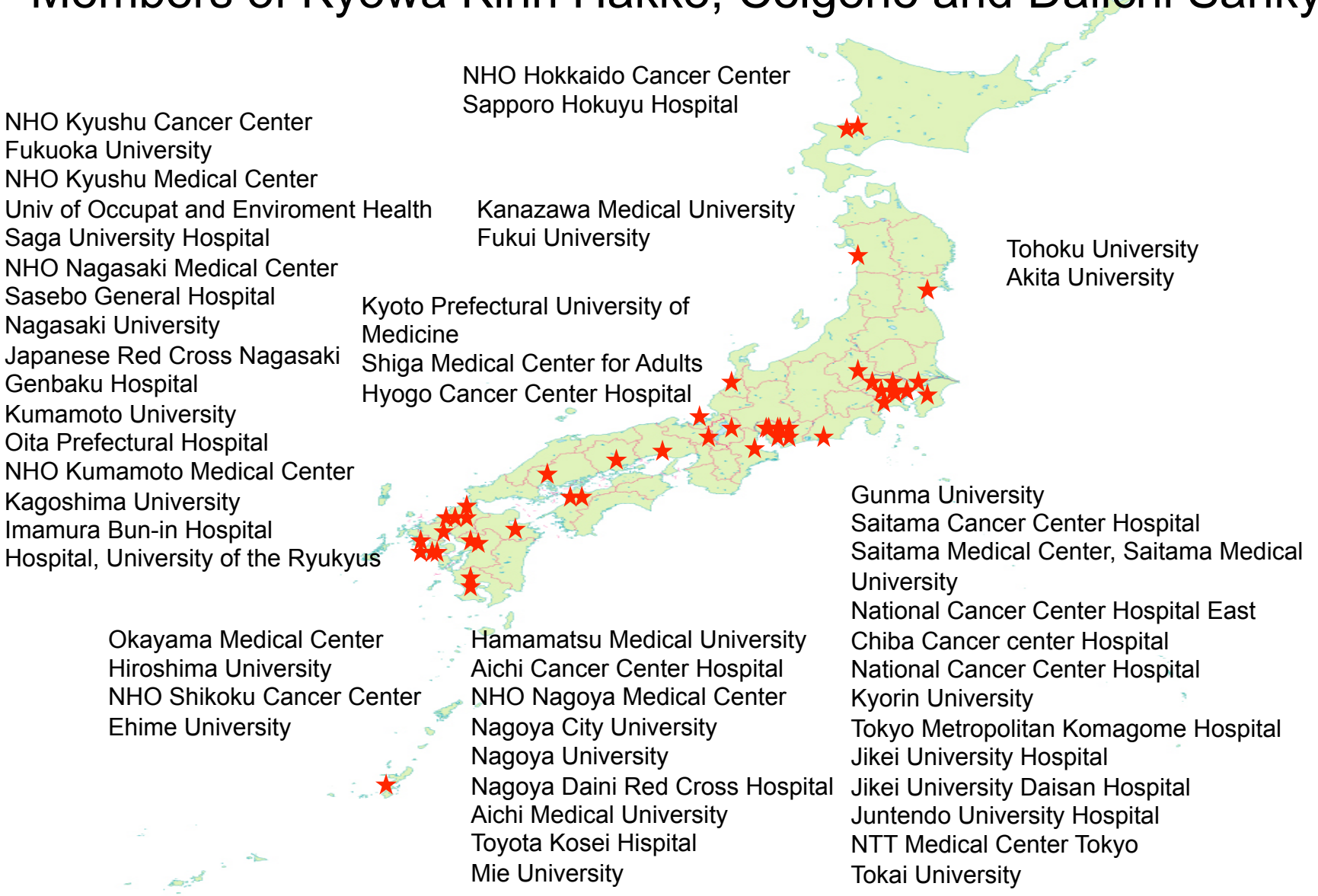
Conclusions and future directions

- Subtype-classification is useful for treatment strategy, however, prognosis is diverse in each subtype of ATL.
- Proposed prognostic index through JCOG trials and nation-wide survey are not sufficient to elucidate very good. prognostic patients who do not require up-front allo-HSCT
- Rapid aging of patients with ATL.
- Molecular/biomarkers for treatment strategies: WW, IFN/ AZT therapy, chemotherapy and allo-HSCT.
- Optimal combination therapies with new agents such as mogamulizmab, lenalidomide and so on.
- Elucidation of resistance-mechanisms to each treatment strategy.
- Continuous clinical trials including global ones for this intractable and rare disease.

Acknowledgements:

JCOG-LSG as shown in below

Members of Kyowa Kirin Hakko, Celgene and Daiichi Sankyo



NHO Hokkaido Cancer Center
Sapporo Hokuyu Hospital

NHO Kyushu Cancer Center
Fukuoka University
NHO Kyushu Medical Center
Univ of Occupat and Enviroment Health
Saga University Hospital
NHO Nagasaki Medical Center
Sasebo General Hospital
Nagasaki University
Japanese Red Cross Nagasaki
Genbaku Hospital
Kumamoto University
Oita Prefectural Hospital
NHO Kumamoto Medical Center
Kagoshima University
Imamura Bun-in Hospital
Hospital, University of the Ryukyus

Kanazawa Medical University
Fukui University

Tohoku University
Akita University

Kyoto Prefectural University of Medicine
Shiga Medical Center for Adults
Hyogo Cancer Center Hospital

Gunma University
Saitama Cancer Center Hospital
Saitama Medical Center, Saitama Medical University
National Cancer Center Hospital East
Chiba Cancer center Hospital
National Cancer Center Hospital
Kyorin University
Tokyo Metropolitan Komagome Hospital
Jikei University Hospital
Jikei University Daisan Hospital
Juntendo University Hospital
NTT Medical Center Tokyo
Tokai University

Okayama Medical Center
Hiroshima University
NHO Shikoku Cancer Center
Ehime University

Hamamatsu Medical University
Aichi Cancer Center Hospital
NHO Nagoya Medical Center
Nagoya City University
Nagoya University
Nagoya Daini Red Cross Hospital
Aichi Medical University
Toyota Kosei Hispital
Mie University