2012...2015. T-Cell Lymphomas: We are illuminating the darkest of tunnels
Monday, April 27, 2015, Royal Hotel Carlton, Bologna, Italy

Conventional and ongoing therapies:

Standard front-line treatment of adult T-cell leukemia-lymphoma (ATL)

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COI Disclosure Information

Kensei Tobinai, MD, PhD, National Cancer Center Hospital

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- Stockholder in: None
- Patents and royalties from: None
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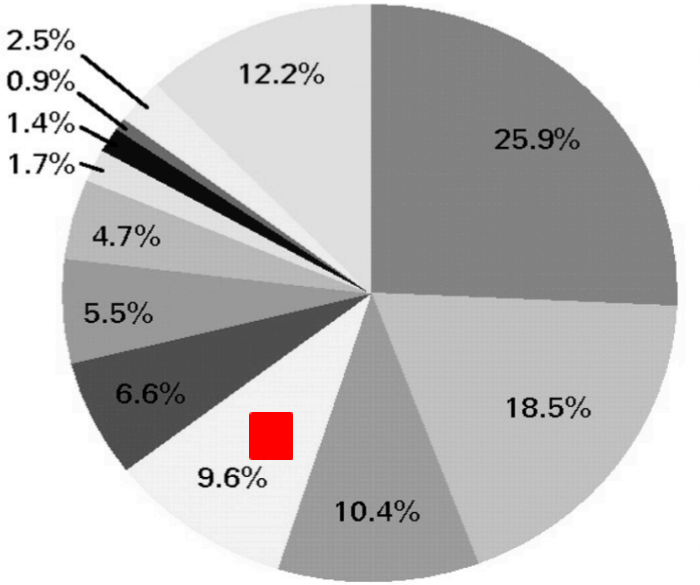
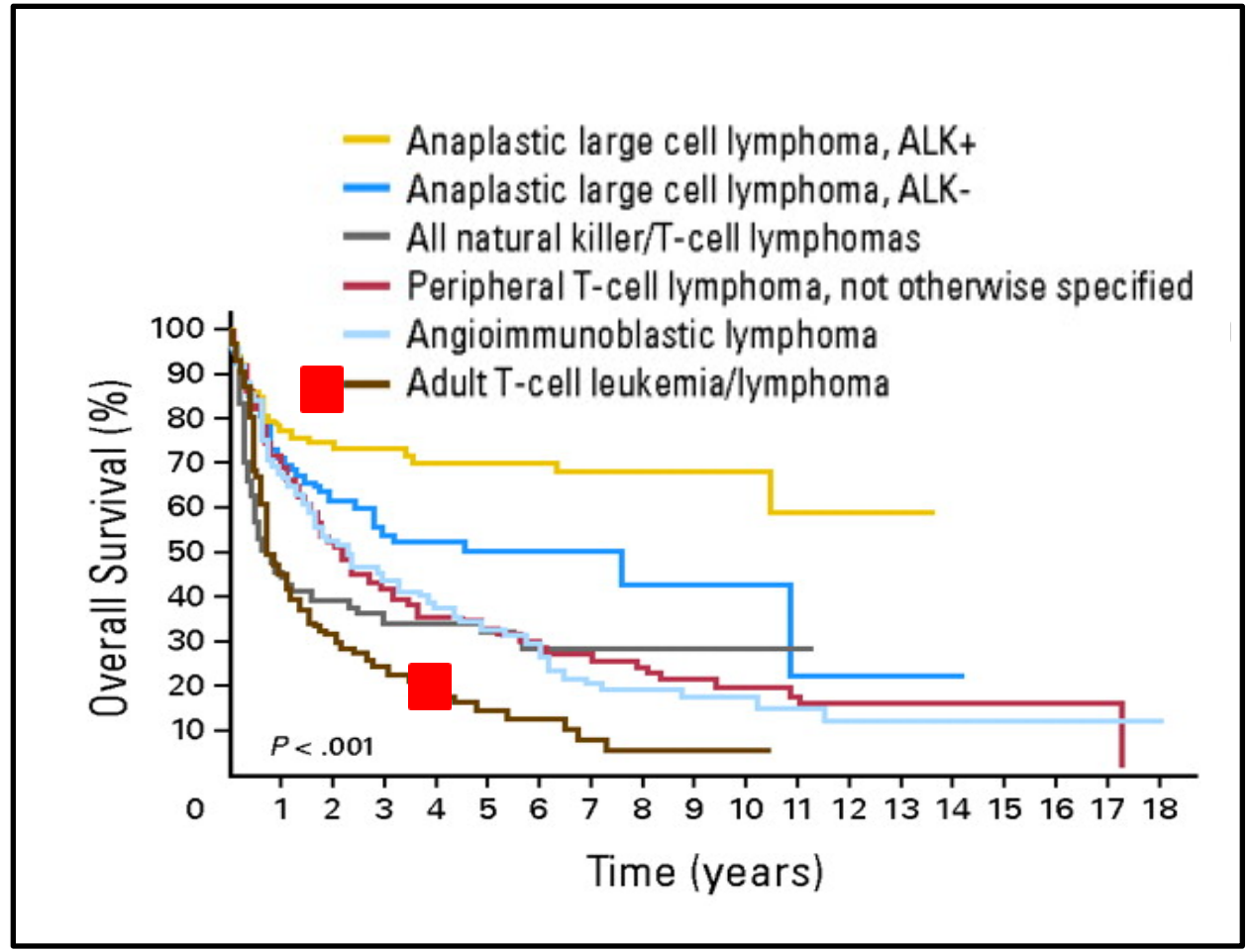
- Other remuneration from: None
- Employee of: None

International T-Cell Lymphoma Project





Vose JM, et al.: International T-Cell Lymphoma Project: J Clin Oncol 2008;26:4124-30

Lymphomas in Japan by the REAL / WHO 1997

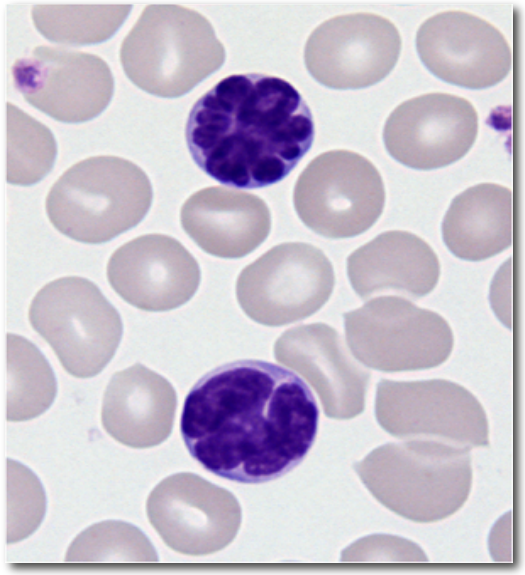
1. **3,194 cases reviewed consisted of 69% of B-NHL, 25% of T/NK-NHL, and 4% of Hodgkin lymphoma.**

2. **Major subtypes of T- or NK-NHL in Japan**
   - **1) 7.5% of adult T-cell leukemia-lymphoma (ATL)**
     19.2% in Kyushu, a south-western island
   - 2) 6.7% of PTCL, unspecified
   - **3) 2.6% of nasal and nasal-type NK/T-NHL**
   - 4) 2.4% of angioimmunoblastic T-cell lymphoma (AITL)
   - 5) 1.5% of ALCL

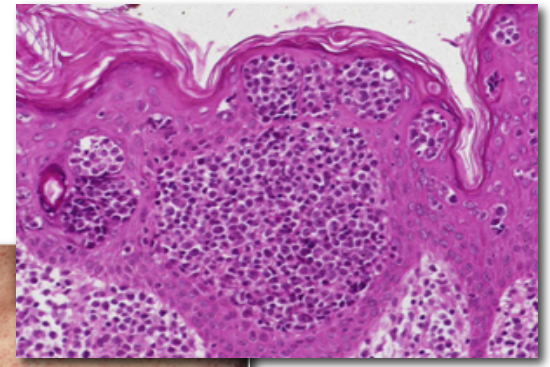
Lymphoma Study Group of Japanese Pathologist: Pathol Int 2000;50:692-702

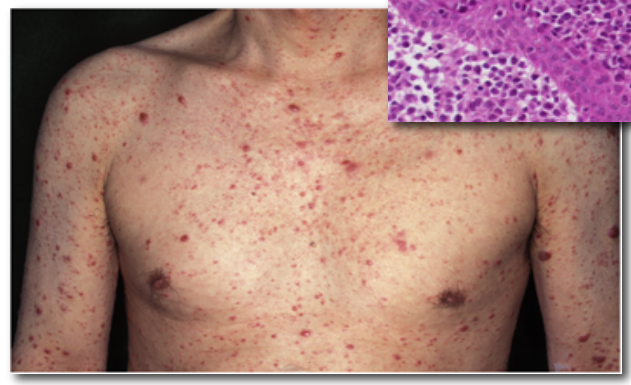
ATL

A neoplasm of Treg;
CD4+, CD25+, CCR4+ and FoxP3+

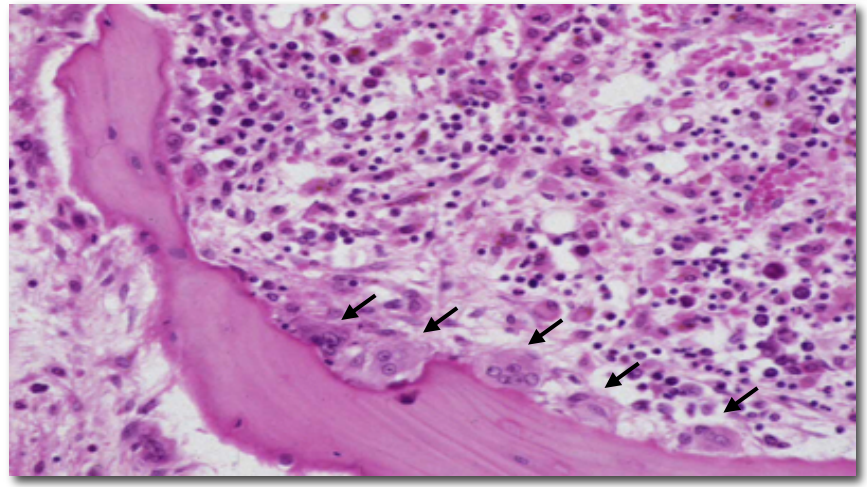


Typical morphology of ATL cells in PB

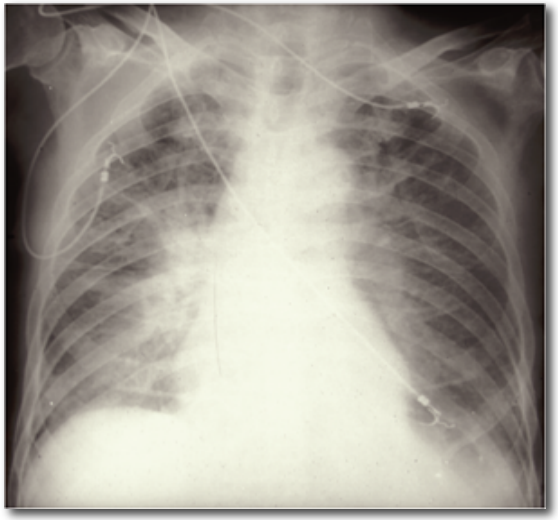




Skin lesions



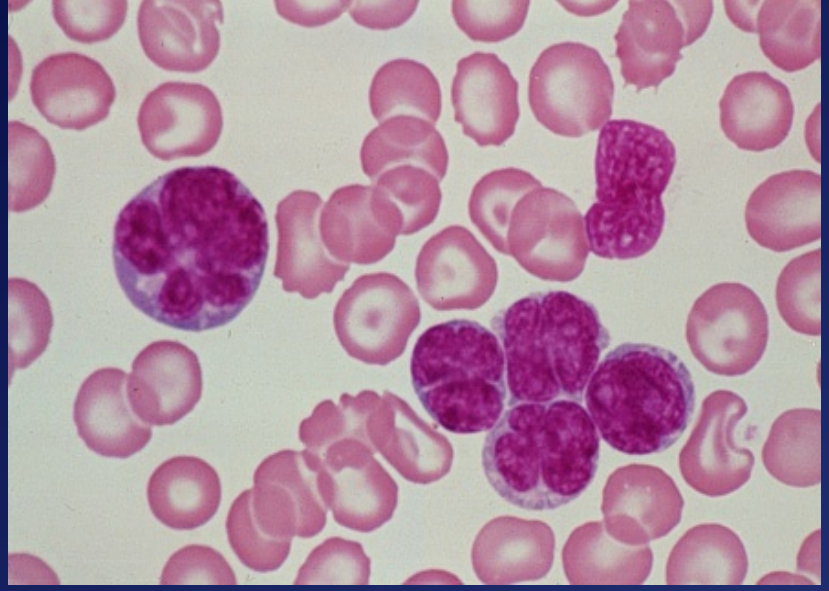
Hypercalcemia



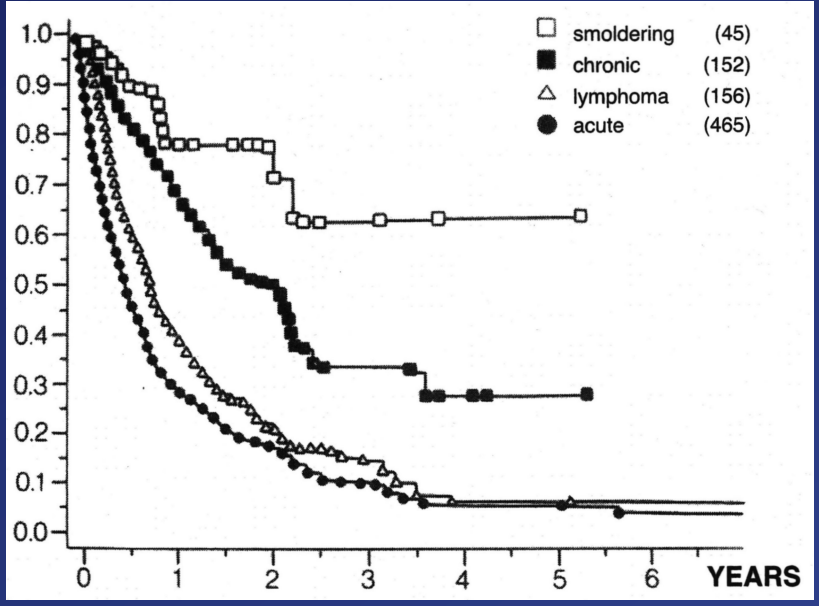
Frequently complicated with opportunistic infections *(Pneumocystis jiroveci, etc.)*

In Japan, there are about 1.2 million HTLV-1 carriers, and about 1,200 HTLV-1 carriers develop ATL each year.

Courtesy of Prof. Matsuoka, Kyoto University, Japan



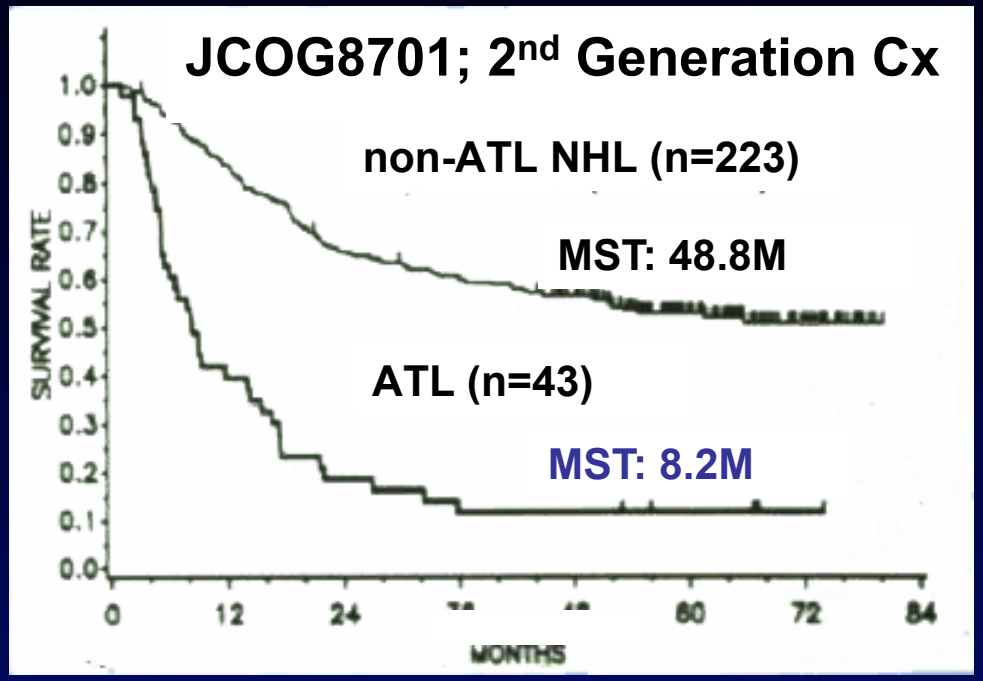
Diagnosis of ATL



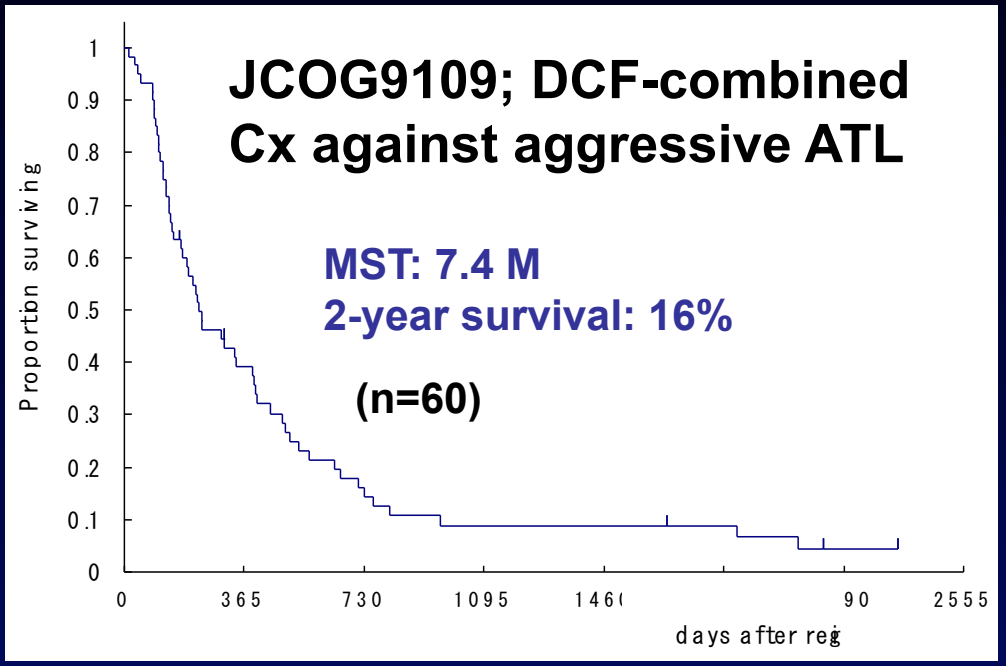
- Acute-type ATL has characteristic findings, including **flower cells in PB, hypercalcemia** and frequent organ involvement (skin, GI-tract, lung, etc.)
- **Regulatory T-cell (Treg) phenotype** (CD4+/8-/25+, CCR4+, FoxP3+)
- Presence of **antibodies to HTLV-1 in serum**
- Four clinical subtypes;
  acute-, lymphoma-, chronic- and smoldering-types

Shimoyama M, et al.: Br J Haematol 1991;79:428–37

Consecutive Clinical Trials for ATL by JCOG-LSG in 1980's to Early 1990's



Tobinai K, et al.: ASCO 1994



Tsukasaki K, Tobinai K, et al.: IJH 2003

Until early 1990's, JCOG-LSG conducted several clinical trials using CHOP-like regimens for aggressive ATL; however, their therapeutic results were disappointing.

VCAP-AMP-VECP;
a G-CSF-Supported, Multiagent Cx in JCOG 9303

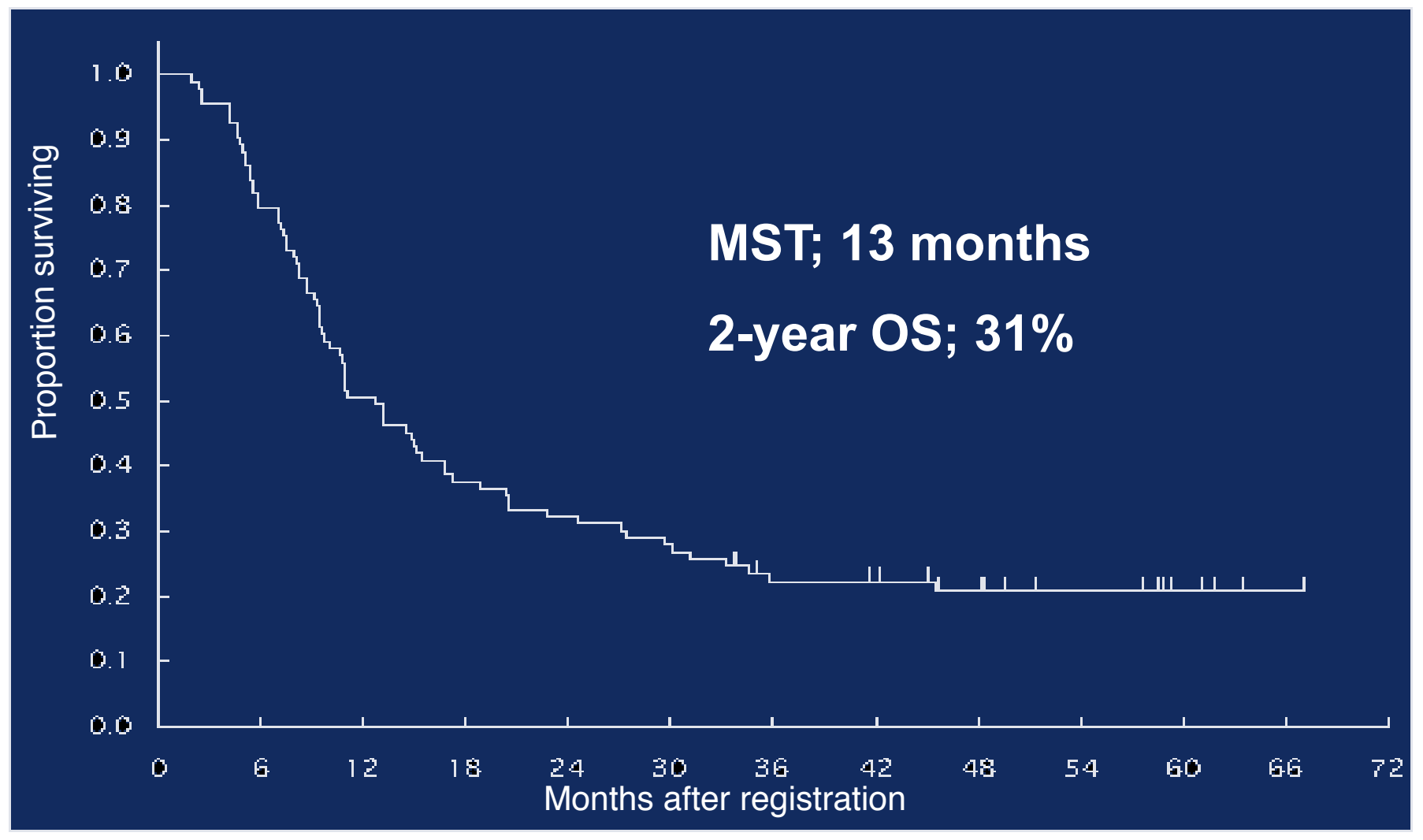
Day		1	8	15 - 17
VCR	1 mg/m²	●		
CPA	350 mg/m²	●		
DXR	40 mg/m²	●	● 30	
PSL	40 mg/m²	●	●	● ● ●
MCNU	60 mg/m²		●	
VDS	2.4 mg/m²			●
ETP	100 mg/m²			● ● ●
CBDCA	250 mg/m²			●

Yamada Y, Tobinai K, et al.: Br J Haematol 2001;114:375-82

every 4 weeks for 7 cycles

IT–MTX + PSL on Cycles 1, 3 & 5

Overall Survival for the 93 Eligible Pts in JCOG9303; a G-CSF-Supported, Multiagent Regimen (VCAP-AMP-VECP)



Yamada Y, Tobinai K, et al.: Br J Haematol 2001;114:375-82

JCOG 9801; a Phase III Study

JCOG
Japan Clinical Oncology Group

Eligibility Check

↓

Informed Consent

↓

Randomization

(A) VCAP-AMP-VECP X 6
- **a) VCAP**
  (G-CSF) 1 wk
- **b) AMP**
  (G-CSF) 1 wk
- **c) VECP**
  (G-CSF) 1 wk

plus IT-MTX/Ara-C
(total 24 wks)

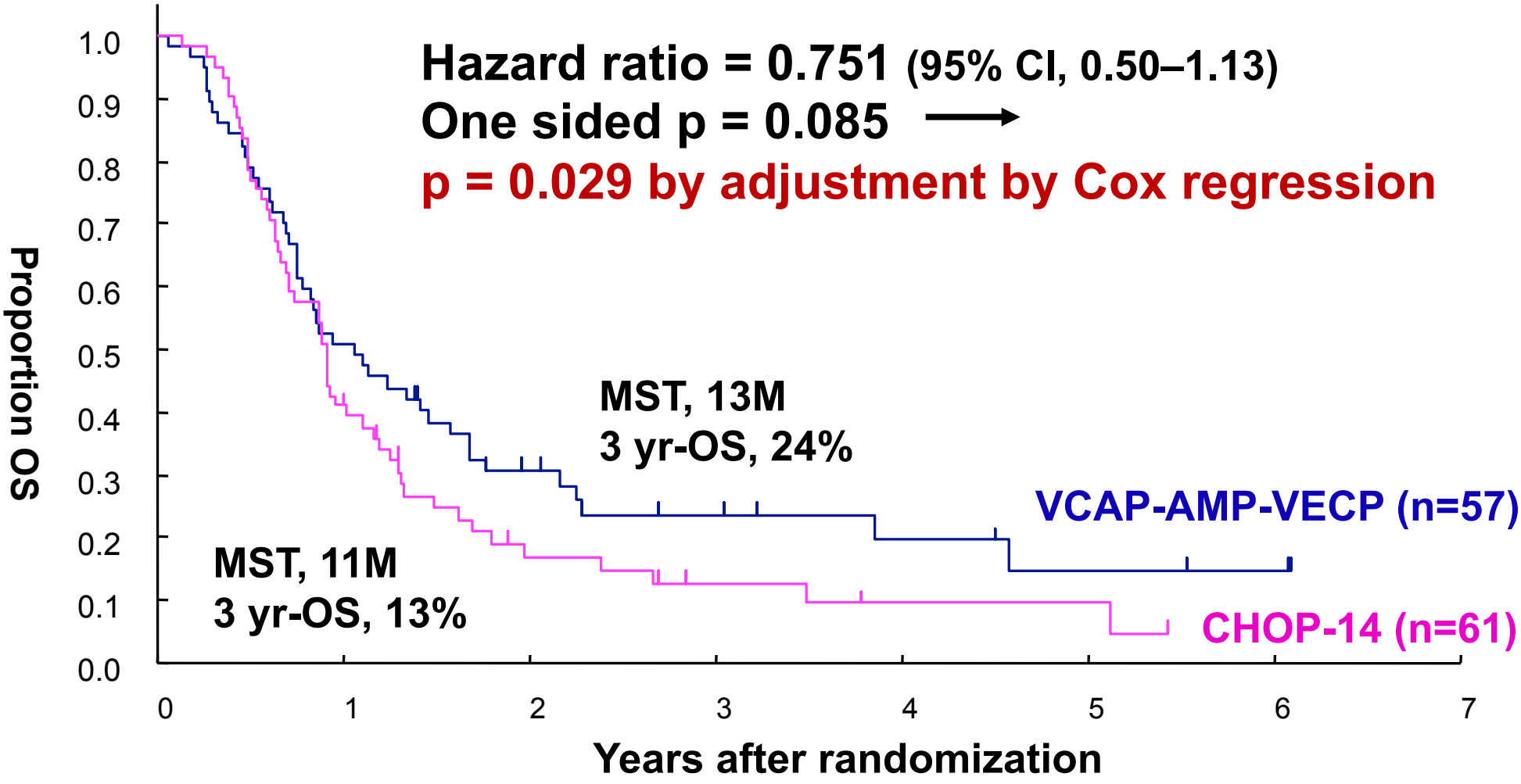
(B) CHOP-14 X 8
(G-CSF) 2 wk
plus IT-MTX/Ara-C
(total 16 wks)

Primary endpoint;
Overall survival

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

Overall Survival of ATL Pts in JCOG 9801

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



VCAP-AMP-VECP, a G-CSF-supported, dose-intensified multi-agent regimen should be the basis for future investigations in the treatment of aggressive ATL.

VCAP-AMP-VECP, a G-CSF-supported, dose-intensified multi-agent regimen should be the basis for future investigations in the treatment of aggressive ATL. However, the MST of 13 months is not satisfactory. Based on the promising results of allo-SCT in a nationwide survey, we are conducting a phase II study of VCAP-AMP-VECP followed by allo-SCT for untreated aggressive ATL (JCOG0907). In addition, we initiated a phase III study to compare AZT/IFN with watchful wait for indolent ATL (JCOG1111).

Tsukasaki K, Tobinai K, et al.: J Clin Oncol 2007;25:5458-64 (JCOG9801)

Tsukasaki K, Tobinai K, et al.: J Clin Oncol 2009;27:453-9 (Int. Consensus Report)

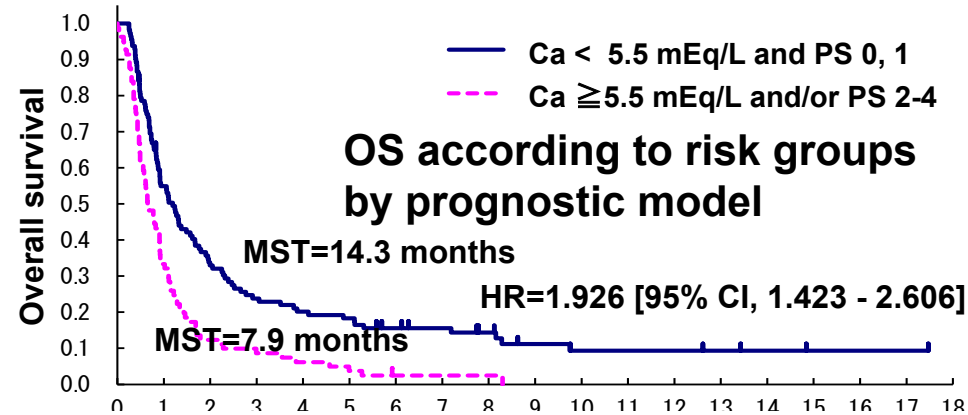
JCOG Prognostic Index (JCOG-PI) and Characterization of Long-Term Survivors of Aggressive ATL (JCOG0902A)

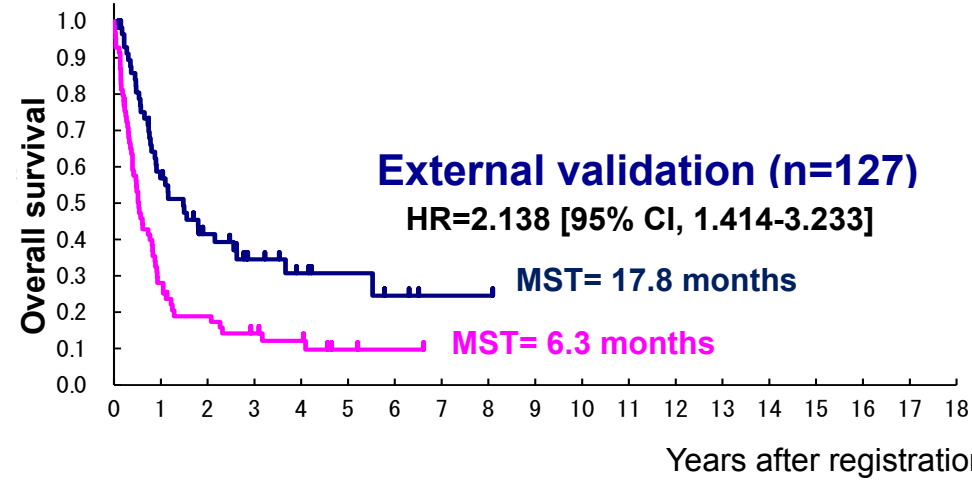
Patients

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

stepwise Cox regression

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



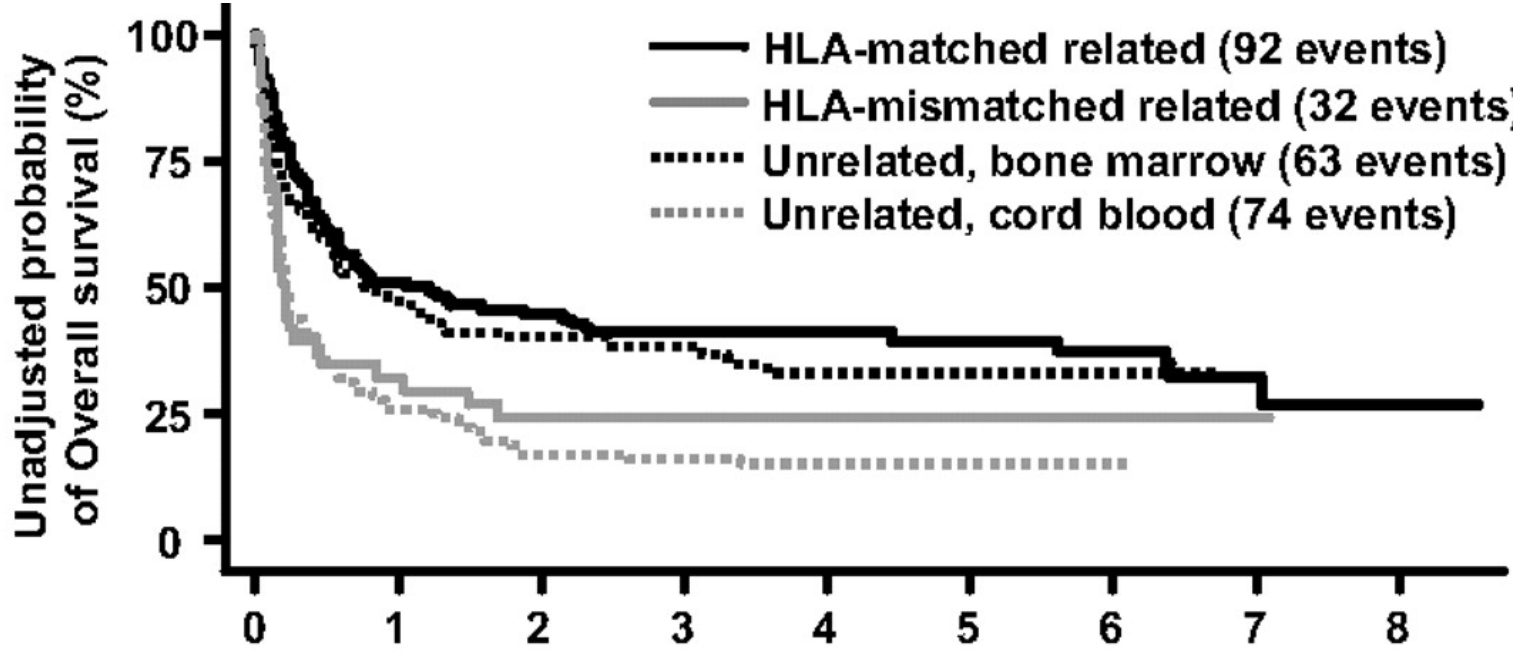


Pts with lymphoma-type who survived >5 years might have been cured. JCOG-PI is valuable for identifying pts with extremely poor prognosis and will be useful for the design of future trials.

Fukushima T, Tobinai K, et al.: Br J Haematol 2014;166:739-48

Allogeneic SCT for ATL: A Nationwide Study in Japan
Overall Survival According to Type of Graft Source

Hishizawa M. et al.: Blood 2010;116:1369-76

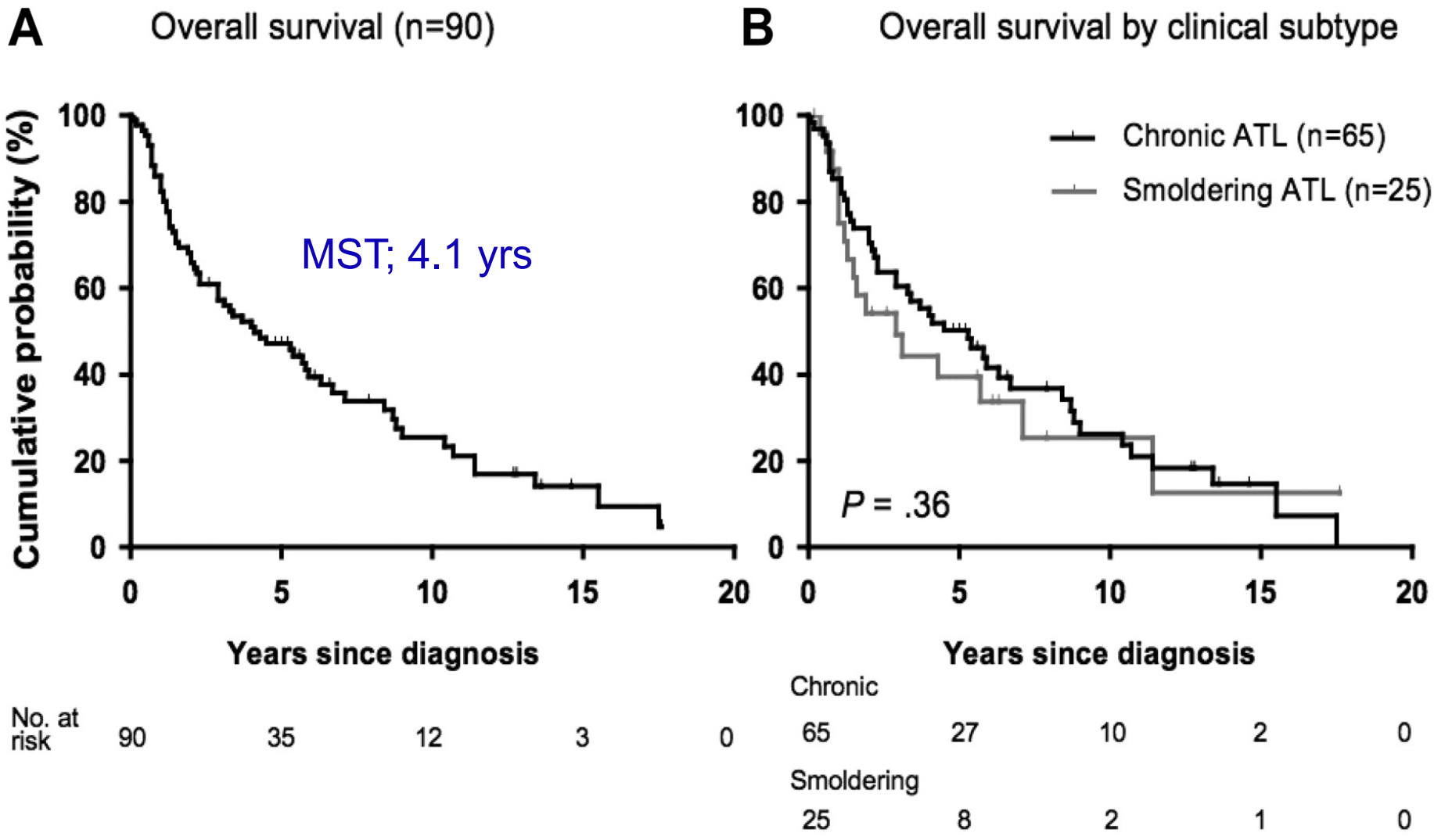


Number at risk									
HLA-matched related	154	75	56	41	30	21	17	7	2
HLA-mismatched related	43	12	9	6	3	3	1	1	0
Unrelated, bone marrow	99	48	36	23	9	4	2	0	0
Unrelated, cord blood	90	22	14	13	8	3	2	0	0

A nationwide study on allogeneic SCT in Japan showed its promising efficacy.

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

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

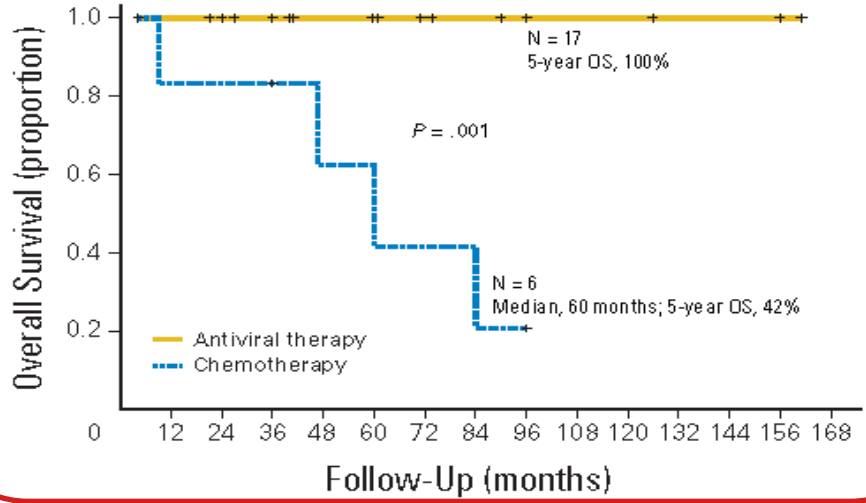


LTFU of indolent ATL pts managed with watchful wait revealed its unfavorable outcome.

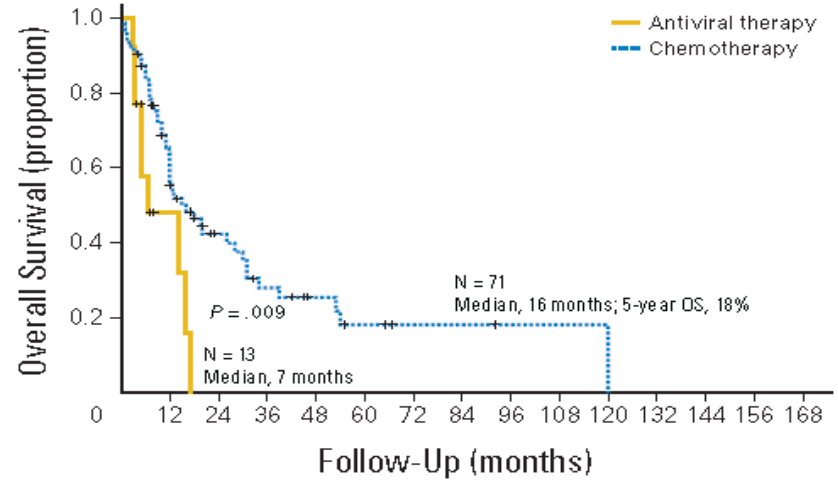
Meta-analysis on Zidovudine and Interferon-alfa (AZT/IFN) in ATL

Bazarbachi A, et al.: J Clin Oncol 2010;28:4177-83

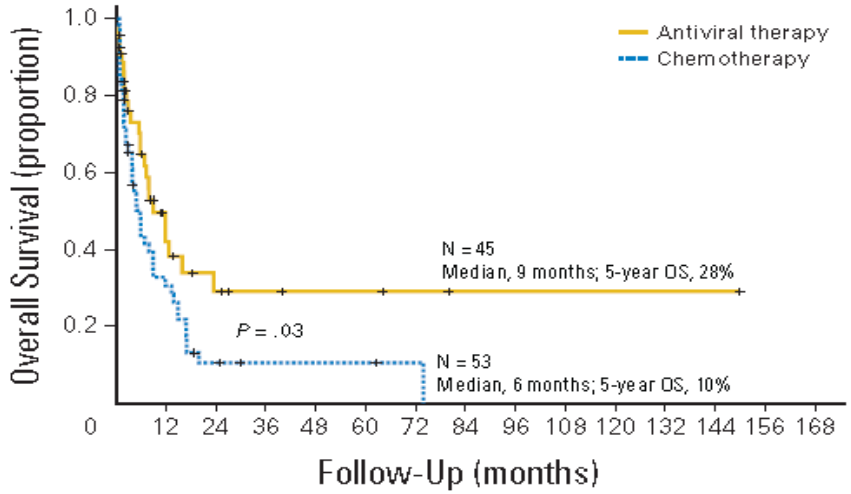
A **Chronic and smoldering**



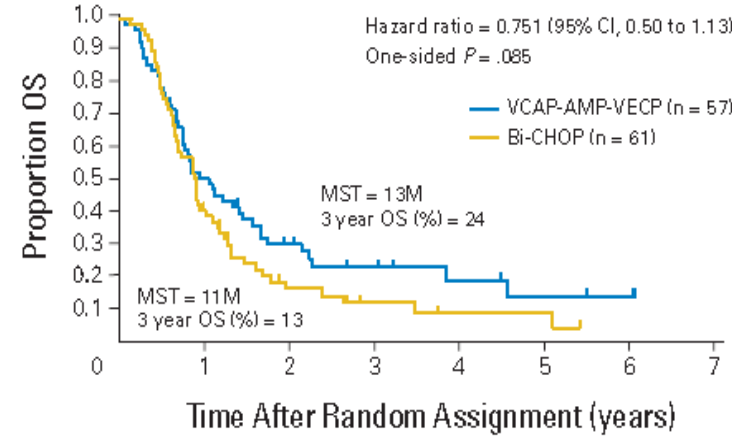
B Lymphoma



C Acute



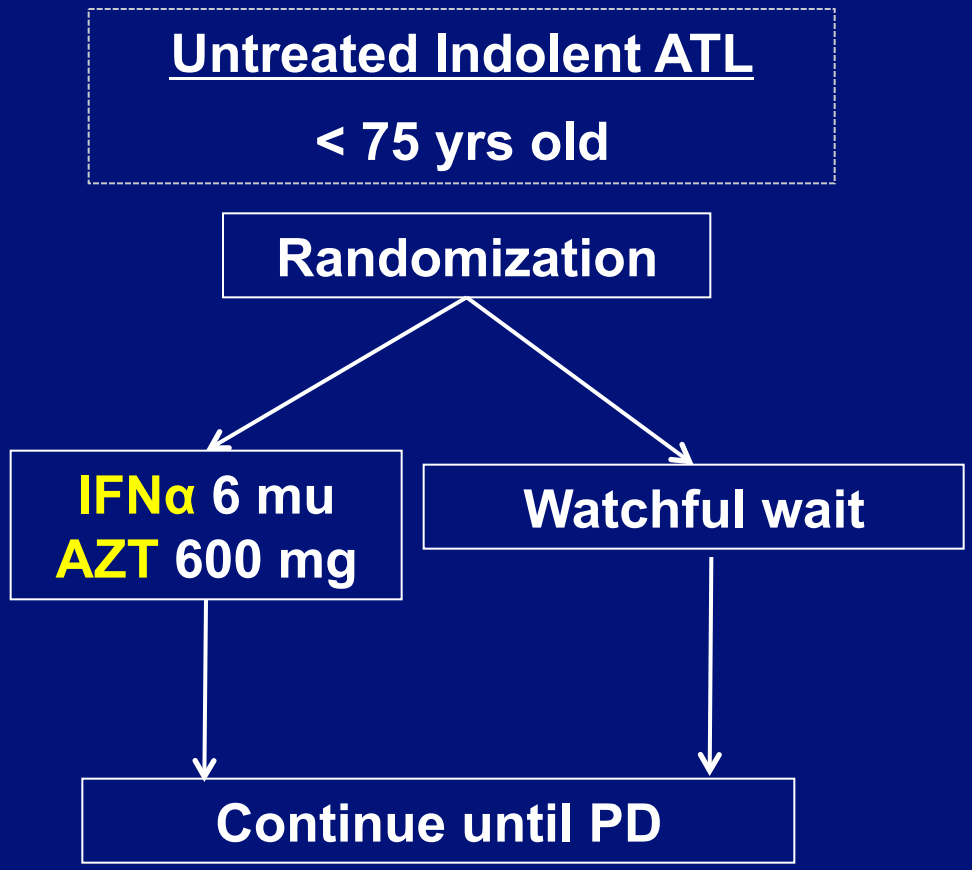
JCOG9801



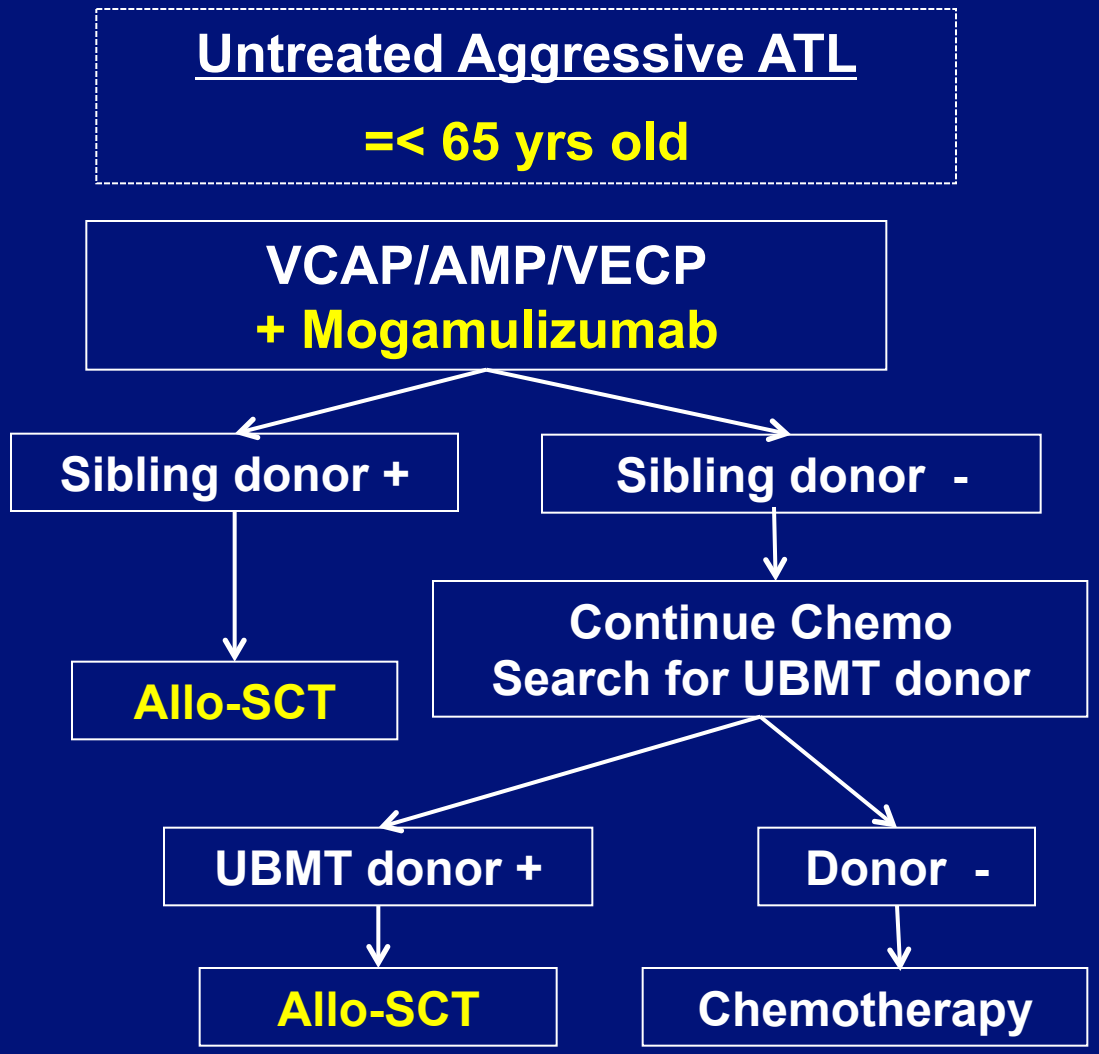
Although AZT/IFN appears promising, especially for pts with leukemic manifestations, caution is needed against the potential selection bias in this kind of retrospective study.

Current Trials for ATL by JCOG-LSG

IFN/AZT v Watchful wait for indolent ATL (pIII: JCOG 1111)



Allo-HSCT for aggressive ATL (pII: JCOG 0907)

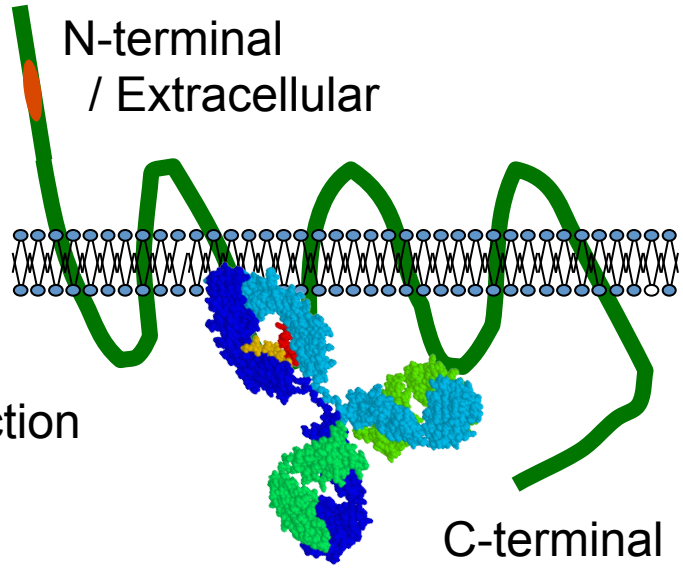


CC Chemokine Receptor 4 (CCR4) & Mogamulizumab

Mogamulizumab

1. High ADCC

3. No direct apoptosis induction



CCR4

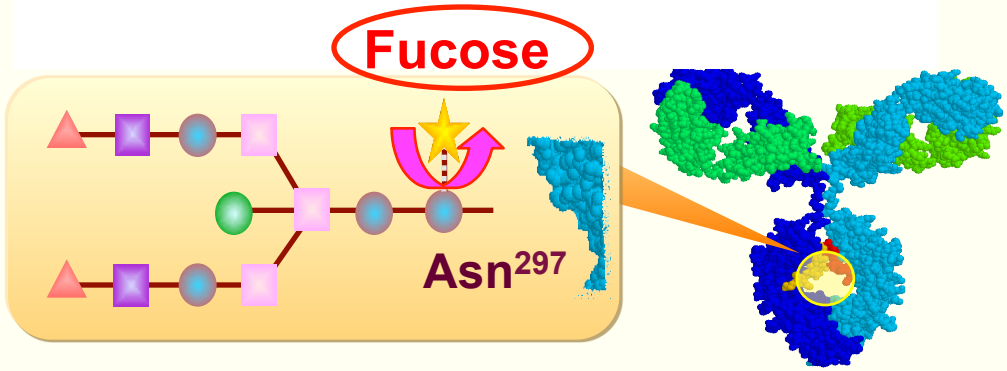
1.7 Transmembrane G protein coupled receptor (GPCR)

2.TARC & MDC as ligands

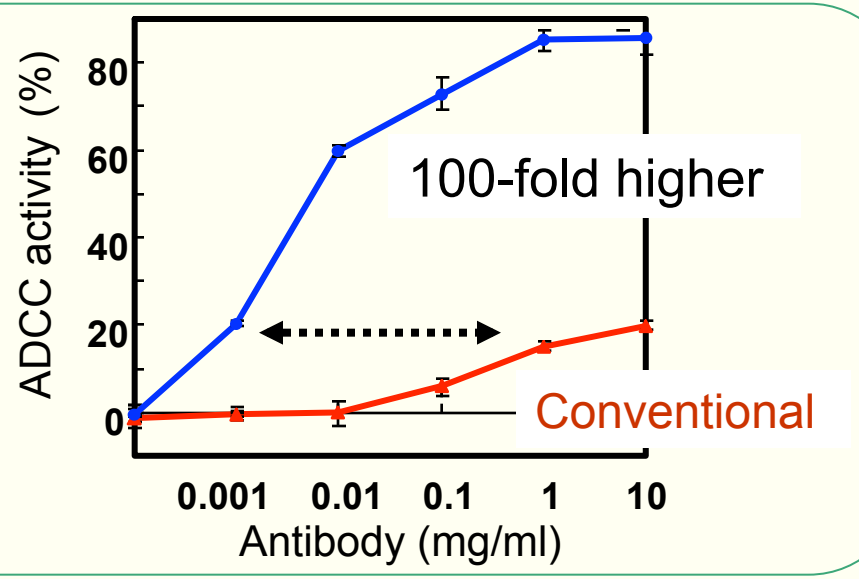
3.Expressed on Th2 cells and FOXP3+ Treg cells

POTELLIGENT® TECHNOLOGY

on the Fc domain



Niwa R, et al.: Cancer Res 2004;64:2127



Efficacy of Mogamulizumab* for Rel/Ref ATL (n=26)

Best overall response (ORR)

		Response					Response rate	
	n	CR***	PR	SD	PD	NE	(%)	[95% CI]
Overall	26	8	5	2	11	0	(50%)	[30 - 70]

50% of ORR (95% CI, 30-70%) met the primary endpoint.

Best response by disease site

Disease site	n	CR	PR	SD	PD	NE	(%)	[95% CI]
Blood	13	13	0	0	0	0	(100%)	-
Skin	8	3	2	0	2	1	(63%)	[25-92)
Nodal & extranodal	12	3	0	4	5	0	(25%)	[6-57]

** Determined according to the criteria described by Tsukasaki et al. (J Clin Oncol, 2009)*

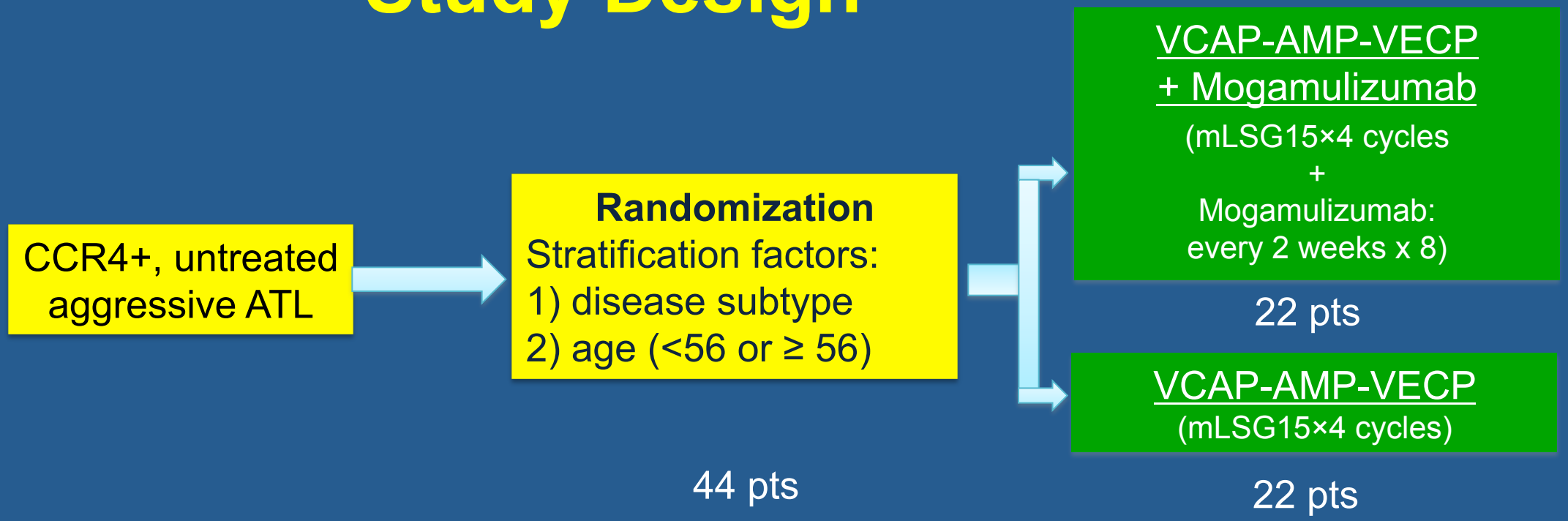
Ishida T, Tobinai K, et al.: J Clin Oncol 2012;30:837-42

Dose-intensified Chemotherapy Alone or in Combination with Mogamulizumab in Untreated Aggressive ATL: a Randomized Phase II Study

Ishida T, Tobinai K, et al.:

Br J Haematol. 2015 Mar 2. doi: [Epub ahead of print]

Study Design



Endpoints: **1. CR rate (%CR)**
2. Overall response rate (ORR),
%CR and ORR according to disease lesion,
PFS, OS, Safety

Ishida T, Tobinai K, et al.: Br J Haematol. 2015 Mar 2. doi: [Epub ahead of print]

Conclusions

Mogamulizumab plus mLSG15

- ✓ Higher %CR than mLSG15 alone (52% vs 33%), meeting the primary endpoint.
- ✓ Well tolerated.
- ✓ Skin disorders were more frequent, but manageable.
- ✓ A reasonable treatment option for untreated ATL.

1) Further investigation is needed mainly because of the small sample size of this randomized phase II study.

2) In addition to its approval for relapsed ATL, PTCL and CTCL, it was approved for untreated ATL on December 18, 2014 in Japan.

Ishida T, Tobinai K, et al.: Br J Haematol. 2015 Mar 2. doi: [Epub ahead of print]

Acknowledgements for ATL Investigators

- **JCOG Studies for ATL**

  Tsukasaki K, Ishitsuka K, Fukushima T, et al.

- **Clinical Trials of Mogamulizumab**

  Ishida T, Ueda R, Akinaga S, Shitara K, et al.

Although the majority of ATL pts are still incurable with the current treatment modalities, we expect that investigations on novel agents and SCT will further improve their outcomes in the near future.