2012…2015.
T-Cell Lymphomas;
We are illuminating
the darkest of tunnels

Bologna
Royal Hotel Carlton
April 27-29, 2015

1) Adult T-cell Leukemia-lymphoma: Mogamulizmab inside the T-cell family

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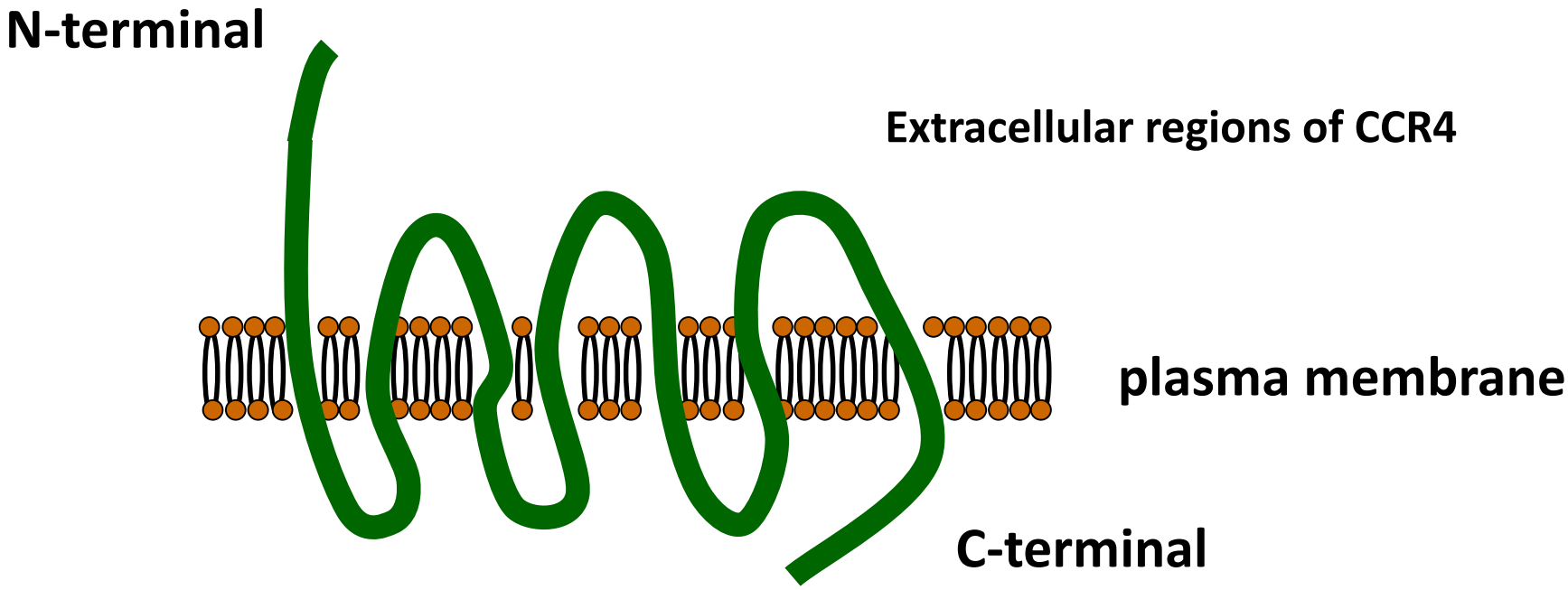
CC chemokine receptor 4 (CCR4)



- The CCR4 gene is located on chromosome 3p24.
- CCR4 is a 7 transmembrane G protein-coupled receptor and consists of 360 aa.
- Expression in normal tissues: some of the T-lymphocytes (Th2/Treg cells) and plts.
- TARC/CCL17 and MDC/CCL22 are ligands of CCR4.

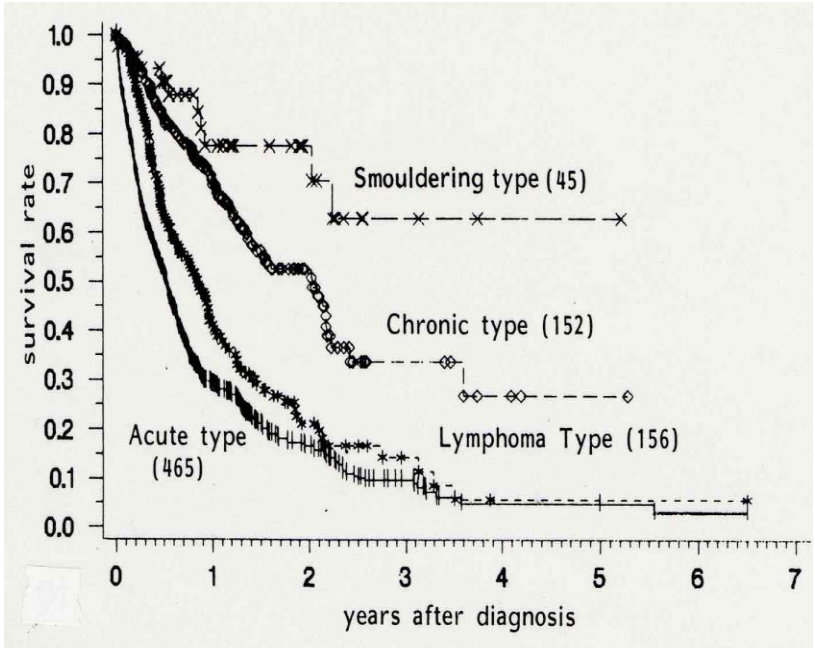
Expression of CCR4 in lymphoma

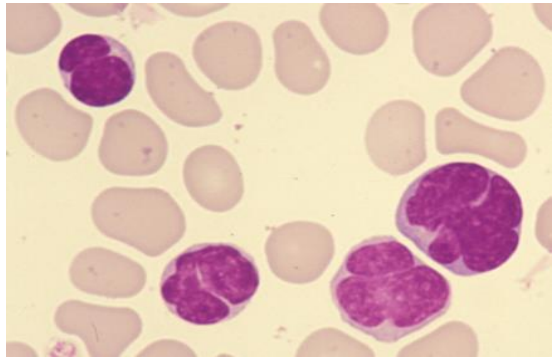
Precursor T-cell Lymphoma		
• Precursor T lymphoblastic lymphoma	0 /4	(0 %)
Mature T-cell and NK-cell Lymphoma		
• Extranodal NK/T lymphoma, nasal type	1 /27	(3.7 %)
• Mycosis fungoides in transformation	10 /20	(50.0 %)
• ALK+ALCL	1 /24	(4.2 %)
• ALK-ALCL	8 /16	(50.0 %)
• PTCL-NOS	24 /58	(41.3%)
• AITL	12 /38	(31.6 %)
• ATL	108 /120	(90.0 %)
Hodgkin Lymphoma		
• Classical Hodgkin Lymphoma	10 /42	(23.8%)
Mature B-cell Lymphoma		
• Diffuse Large B-cell lymphoma	2 /53	(3.8%)

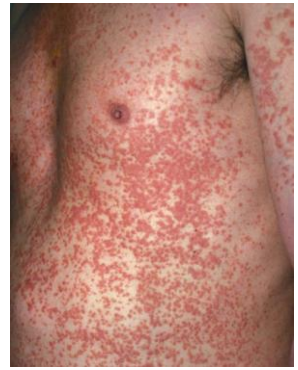
Ishida et al, Clin Cancer Res 2003;9:3625

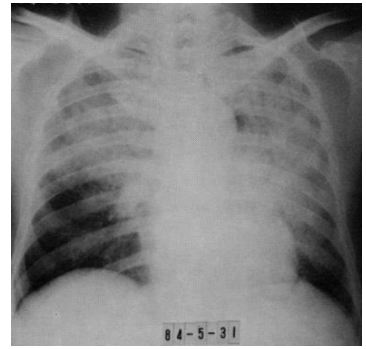
Adult T-cell leukemia-lymphoma（ATL）

- 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





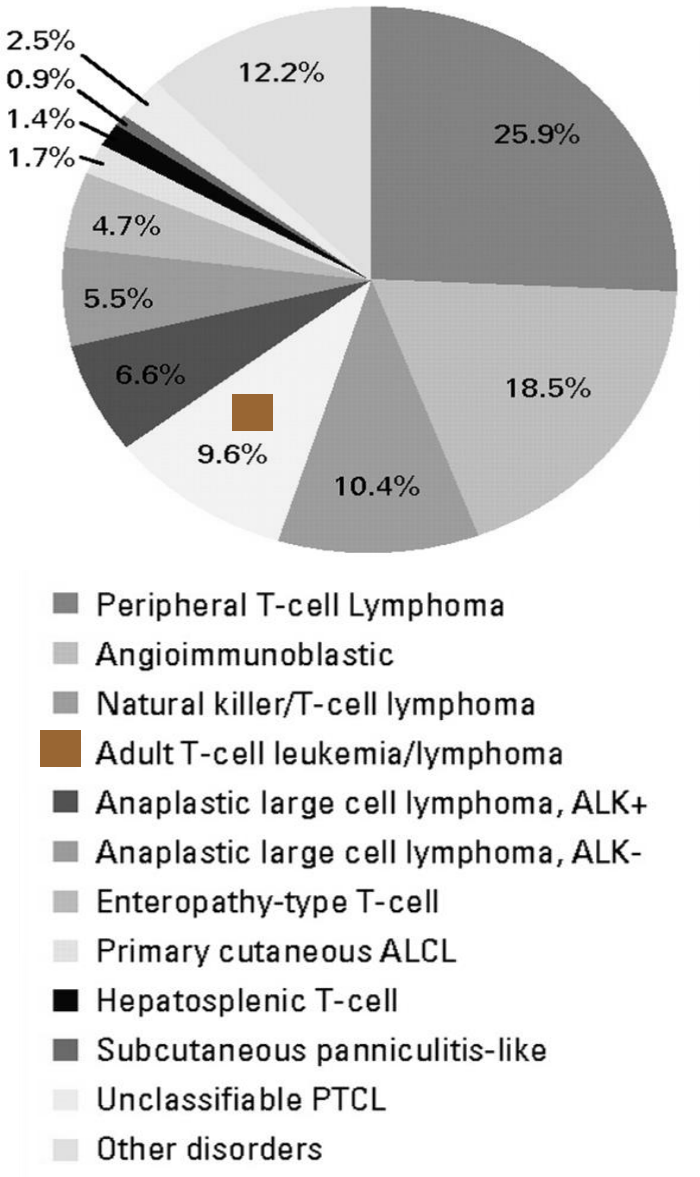


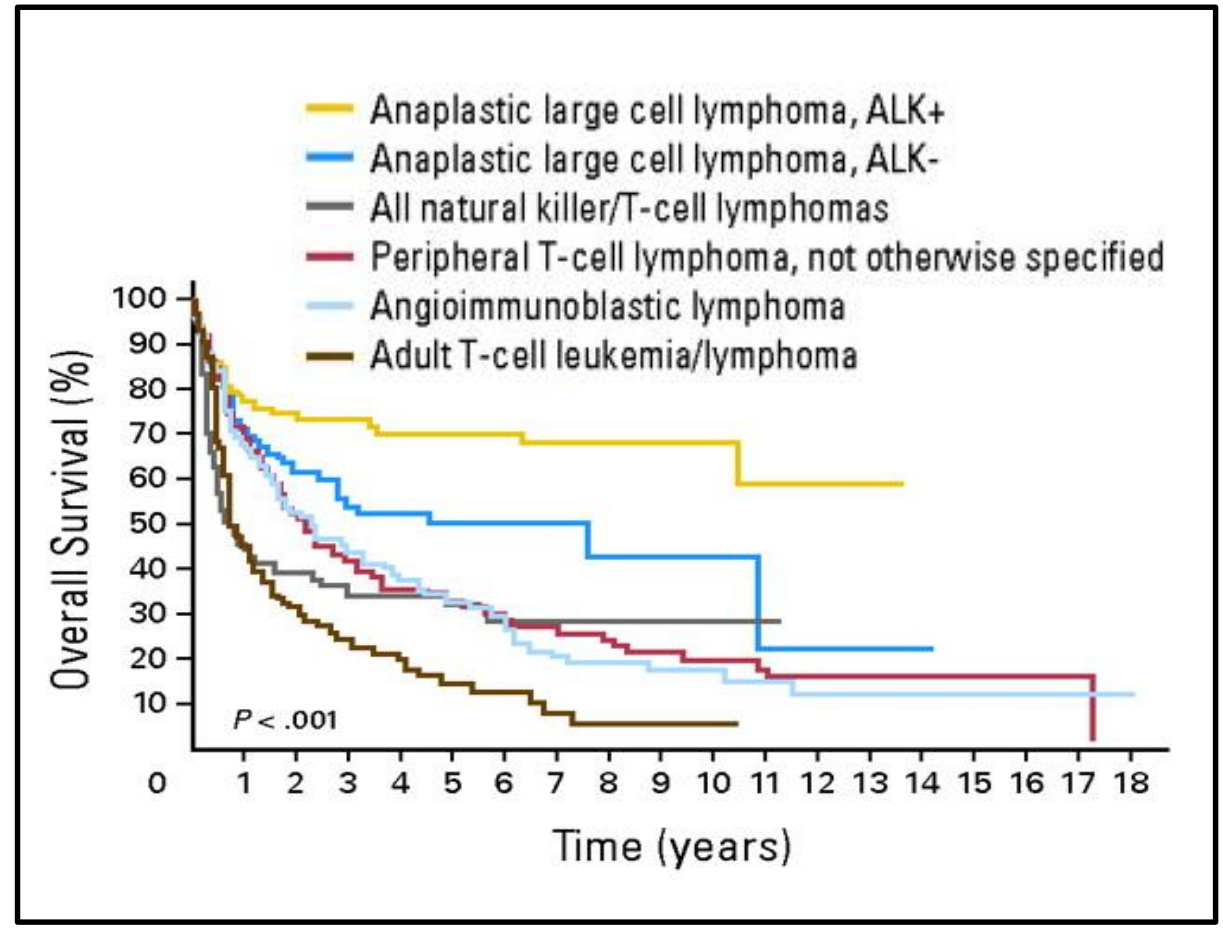


Clinical subtype	Smoldering/Chronic	Acute/Lymphoma
Organ involvement	No/Minimum (skin etc)	Yes
LDH level	Normal or raised=<x2	Raised>x2
Calcium level	Normal	Raised
Median survival time	> 24months	6-10 months

Shimoyama et al. Br J Haematol, 1991

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

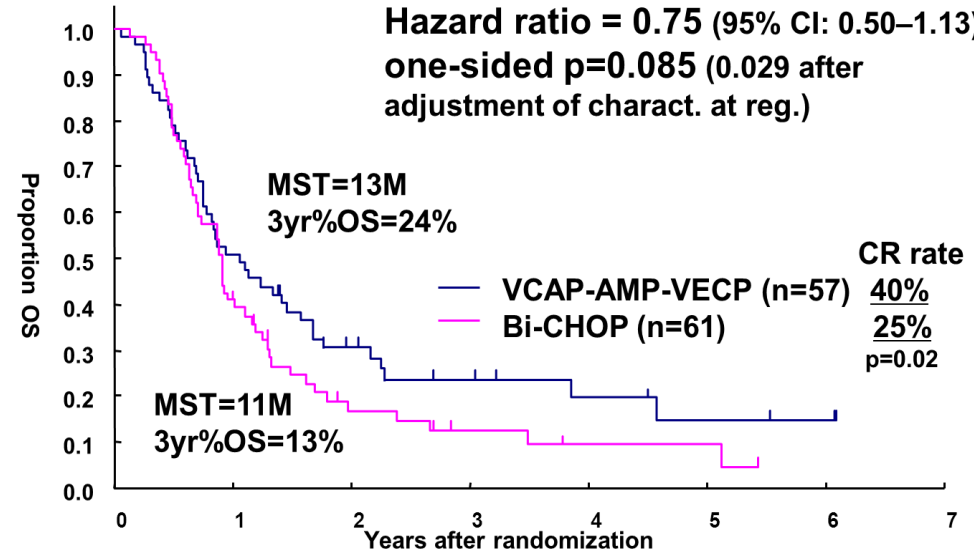
P-Ⅲ study of VCAP-AMP-VECP vs. CHOP-14 in aggressive ATL:JCOG9801

Aggressive ATL, age<70
acute-, lymphoma- or unfavorable chronic

↓

Randomization
Stratification; Institution, PS (0,1/2-4)

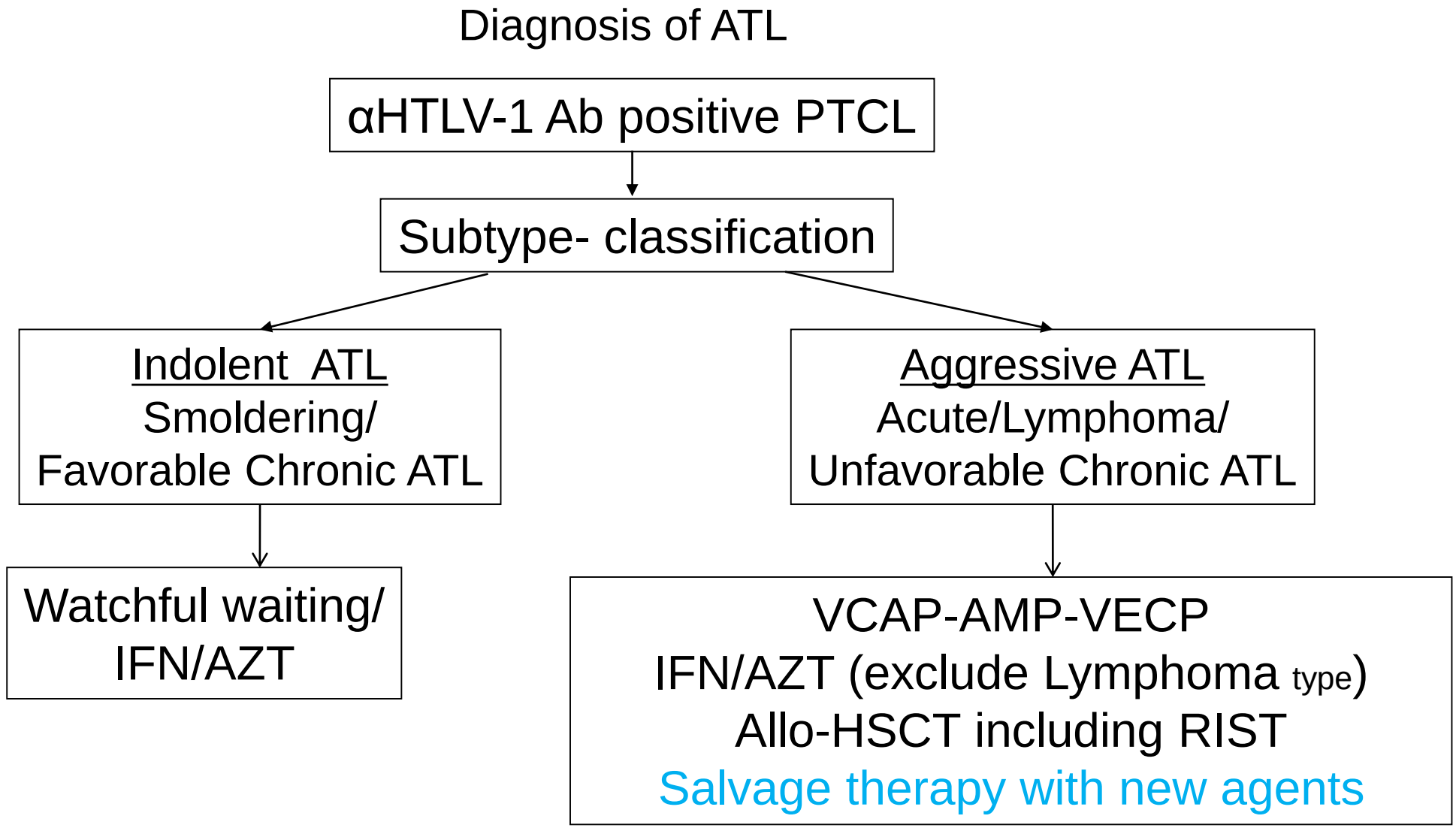
CHOP-14	VCAP→AMP→VECP
x 8 cycles	x 6 cycles
with G-CSF and IT x 3 of Ara-C, MTX and PSL	with G-CSF and IT x 3 of Ara-C, MTX and PSL



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

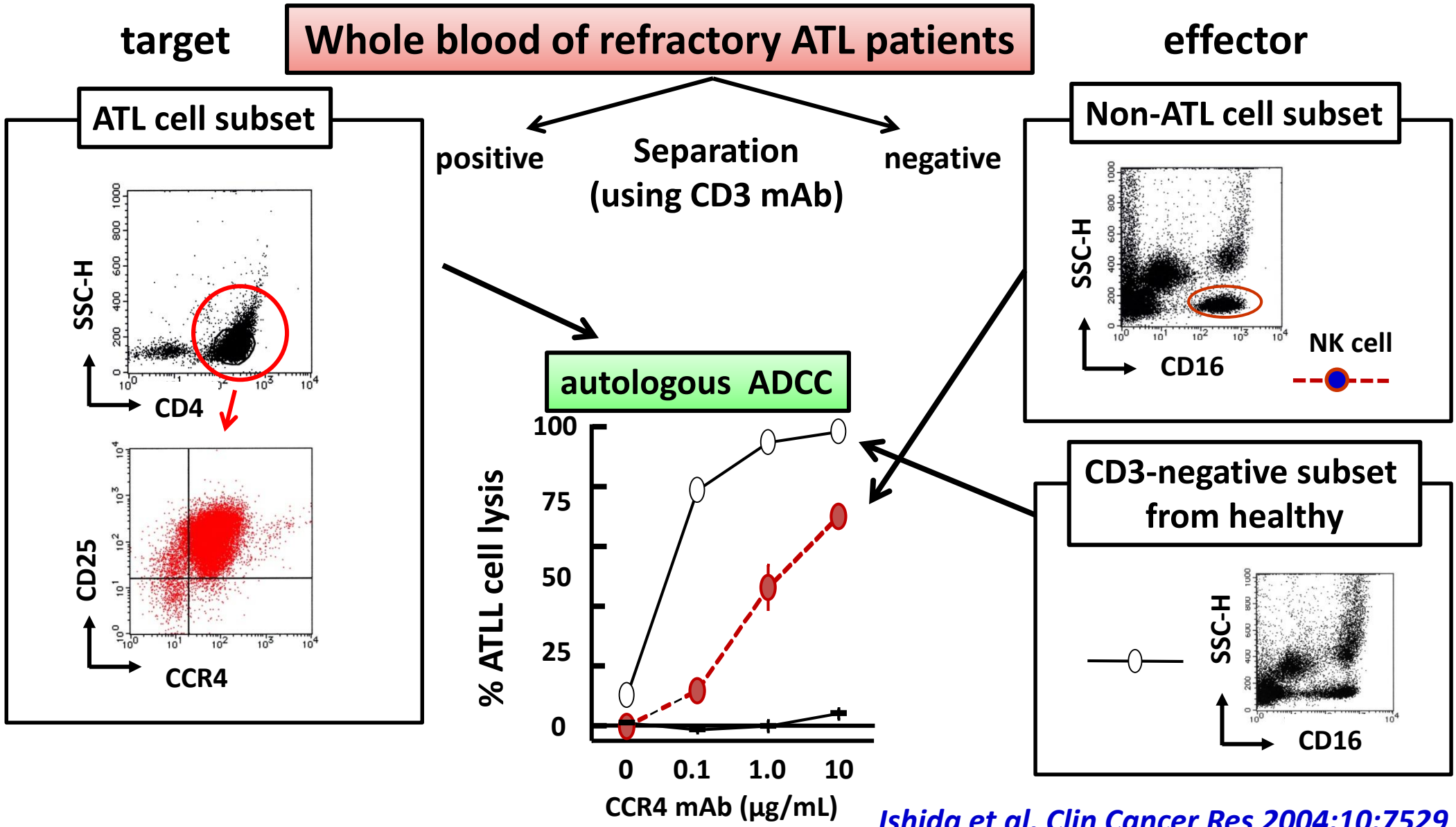
Tsukasaki K, Tobinai K, et al. J Clin Oncol, 2007

Recommended strategy for consideration on the treatment of ATL



ATL consensus Report; Drs from Brazil, France, Lebanon, Japan, UK and USA; JCO2009

Humanized anti-CCR4 mAb-induced ADCC activity against ATL cells obtained from patients tested in an autologous setting.



Ishida et al, Clin Cancer Res 2004;10:7529

P-I study of Mogamulizumab, a defucosylated anti-CCR4 Ab, in relapsed pts with ATL or peripheral T-cell lympoma (PTCL)

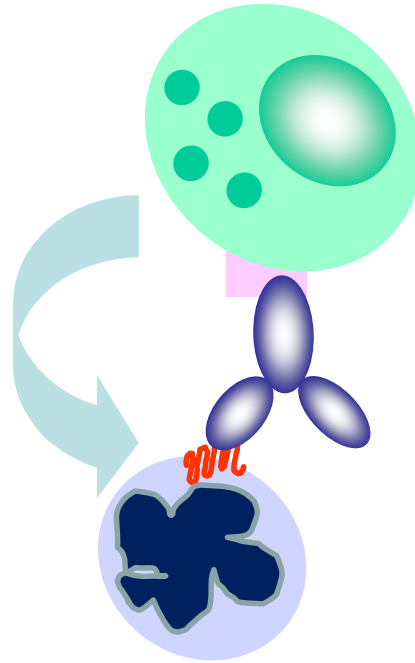
Concept

A therapeutic antibody which binds to a chemokine receptor, CCR4, eliminates the target cells expressing CCR4 protein through a cytolytic action, ADCC.

ADCC

Antibody-dependent cellular cytotoxicity

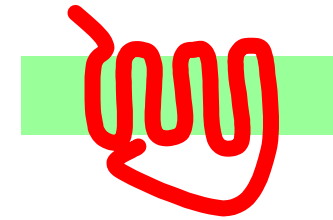
- **One of the most important functions of the therapeutic antibodies**
- **Development of a first-in-class zero-fucose humanized antibody with high ADCC activity targeting CCR4**



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)**



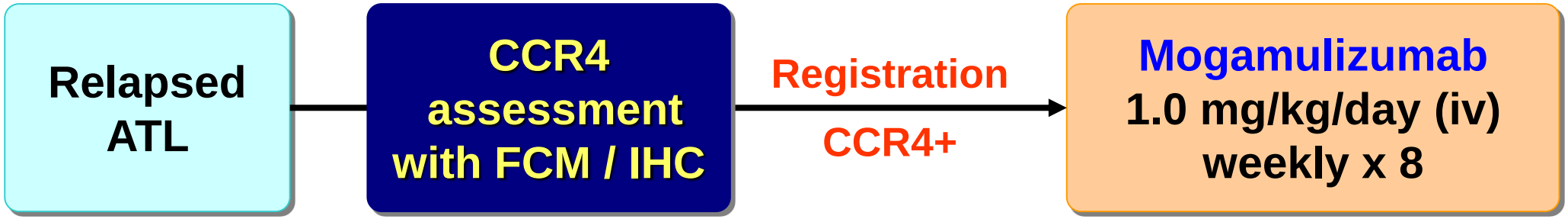
- **MTD was not reached until 1mg/kg in 16 pts.**
- **RR was 31% including 2 CRs among 13 ATL patients.**

→ **Recommended phase II dose: 1.0 mg/kg**

Yamamoto K, Tsukasaki K, Tobinai K et al. JCO 20

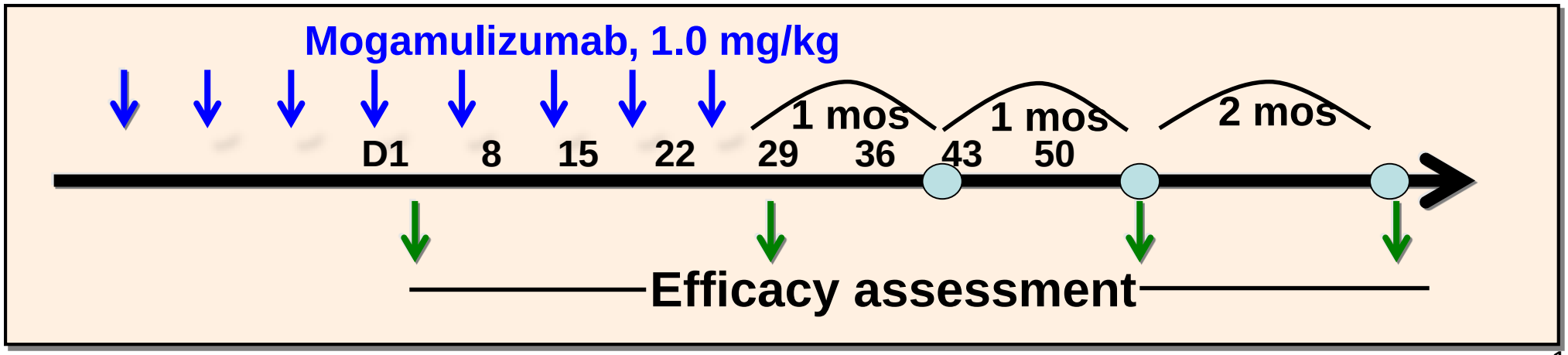
Phase II study of Mogamulizumab in relapsed ATL

A multicenter open labeled study

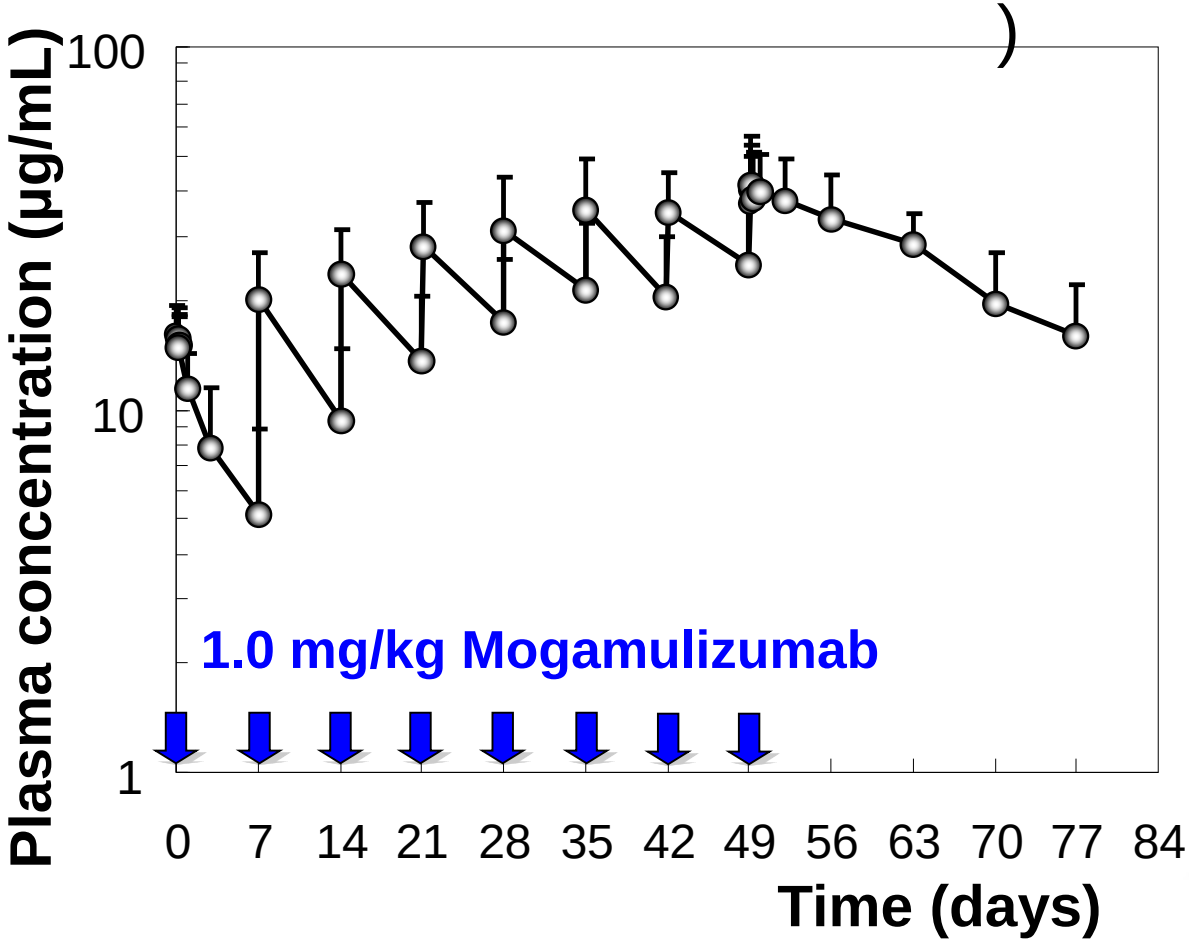


Primary endpoint; Overall response rate

Dosing and assessment schedule

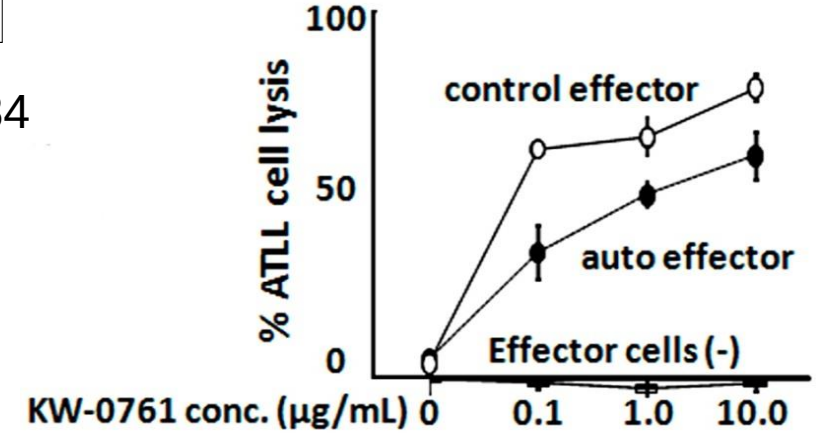


Pharmacokinetics:
P2 study of Mogamulizumab in relapsed aggressive ATL



PK parameters	(After 8th infusion)
C_{max} (μg/mL)	42.9±14.2
C_{trough} (μg/mL)	33.6±10.6
$AUC_{0\text{-}7days}$ (μg·h/mL)	6297±1812
$t_{1/2}$(h)	422±147

Autologous Mog- induce ADCC



No anti-Mogamulizumab antibody was detected in all pts

Ishida T, Tsukasaki K, Tobinai K, et al. JCO 2012

Ishida et al, Clin Cancer Res 2010

Adverse events (n=27)*

gP-2 study of Mogamulizumab in relapsed aggressive ATL

Non-Hematologic AEs	Grade 3	Grade 4	All grades
Acute infusion reaction	1	0	24
Rash	5	0	17
ALT	2	0	11
AST	2	0	10
Hypoxia	3	0	5
γ-GTP	3	0	4
Pruritus	1	0	4
Hypokalemia	2	0	3
Hypercalcemia	0	1	3
Erythema multiforme**	1	0	1
Hyperglycemia	1	0	1
Tumor lysis syndrome	1	0	1
Metabolic/Lab-other (LDH etc.)	3	0	14

Hematologic AEs	Grade 3	Grade 4	All grades
Lymphopenia***	9	11	26
Leukocytopenia	8	0	18
Thrombocytopenia	3	2	14
Neutropenia	5	0	14
Hemoglobin	1	0	8

CTCAEv3.0
* Possibly/probably/definitely drug-related
** Stevens-Johnson syndrome
*** Includes abnormal lymphocytes

Ishida T, Tsukasaki K, Tobinai K, et al. JCO 2012

Efficacy assessment*
P-2 study of Mogamulizumab in relapsed aggressive ATL

Disease site	n	Best response					Response rate		
		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]

*** Determined according to the criteria described by Tsukasaki et al. (*J Clin Oncol 2009;27:453*)**

**** One pt with concurrent colon cancer was excluded**

Ishida T, Tsukasaki K, Tobinai K, et al. JCO 2012

Efficacy assessment*
P-2 study of Mogamulizumab in relapsed aggressive ATL

Disease site	n	Best response					Response rate		
		CR	PR	SD	PD	NE	≥ PR	(%)	[95% CI]
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Overall	26	8	5	2	11	0	13	(50 %)	[30-70]

* I
20
**

1st line CTx (mLSG15 + mLSG19) for aggressive ATL in the JCOG 9801 study #

	Lymphoma	Acute	Unfavorable chronic
CR (# of all pts) (95%CI)	54% (14/26) (33-73%)	27% (22/81) (18-38%)	18% (2/11) (8-52%)

Tsukasaki K, Tobinai K, et al. J Clin Oncol, 2007

Conclusions:
PII study of Mogamulizumab in relapsed aggressive ATL

- **26 of 27 pts received 1. 0 mg/kg of Mogamulizumab were evaluable for efficacy analysis.**
- **50% of ORR (13/26; 95% CI, 30 - 70) met the primary endpoint defined as the best overall response (Threshold; 5%, Expected; 30%).**
- **Most common adverse events were acute infusion reaction, rash, ALT increase, AST increase, hypoxia and hematologic toxicities.**
- **Grade 3 rash was observed in 5 pts. However, they were recovered or recovering by steroid-treatments.**
- **Pharmacokinetic analysis showed that the concentrations sufficient to exert ADCC against ATL could be clinically achieved.**
- **No anti-Mogamulizumab antibody was detected in all pts.**

Mogamulizumab is an effective agent with acceptable toxicity profiles for pts with relapsed aggressive ATL.

Ishida T, Tsukasaki K, Tobinai K, et al. JCO 2012

Dose-intensified chemotherapy alone or in combination with mogamulizumab in newly diagnosed aggressive ATL: a randomized phase II study

CCR4 positive newly diagnosed ATL

1:1 Randomization

[1st stratification factor]

Disease subtype

(acute, lymphoma or unfavorable chronic)

[2nd stratification factor]

Age (<56 or ≥ 56)

VCAP-AMP-VECP arm

(mLSG15 × 4cycles)

Open-label design

VCAP-AMP-VECP + Mogamulizumab arm

(mLSG15 × 4cycles
+
Mogamulizumab: every 2 weeks x 8)

mLSG15	(mg/m²)			Day 1	8	15	22	29
VCAP								2nd cycle
VCR	1		IV	↓				
CPA	350		IV	↓				
ADM	40		IV	↓				
PSL	40	(mg/m²)	PO	↓				
AMP								
ADM	30		IV		↓			
MCNU	60		IV		↓			
PSL	40	(mg/m²)	PO		↓			
VECP								
VDS	2·4		IV			↓		
ETP	100		IV			↓↓↓		
CBDCA	250		IV			↓		
PSL	40	(mg/m²)	PO			↓↓↓		
Ara-C	40		IT					↓†
MTX	15		IT					↓†
PSL	10	(mg)	IT					↓†
Mogamulizumab	1·0	mg/kg	IV	↓†		↓‡		↓§

Primary end point;
%CR

Secondary end points;
ORR, PFS, OS, safty

Ishida T, Tobinai K, et al. BJH 2015

Patients Characteristics:
Chemo. alone vs. Chemo.+ mogamulizmab: a randomized phase II study

	mLSG15 + mogamulizumab (n = 29)	mLSG15 (n = 24)*
ATL subtype		
Acute	20 (69%)	17 (71%)
Lymphoma	6 (21%)	7 (29%)
Unfavorable chronic	3 (10%)	0 (0%)
Age, year		
Median	61	64
Range	49-81	37-74
<56	11 (38%)	6(25%)
>=56	18 (62%	18 (75%)
Sex		
Male	12 (41%)	16 (67%)
Female	17 (59%)	8 (33%)
ECOG PS		
0	16 (55%)	13 (54%)
1	10 (35%)	9 (38%)
2	3 (10%)	2 (8%)

Ishida T, Tobinai K, et al. BJH 2015

Adverse Events
Chemo. alone vs. Chemo.+ mogamulizmab: a randomized phase II study

Most common treatment-related AEs

AEs (CTCAEv4.0)	Patients affected, N			
	mLSG15 + Mogamulizumab (n=29)		mLSG15 (n=24)	
Preferred Term	All Grades	Grade ≥3	All Grades	Grade ≥3
Neutropenia	100%	100%	96%	92%
Thrombocytopenia	100%	90%	96%	71%
Leukopenia	100%	100%	92%	88%
Lymphopenia	97%	97%	96%	75%
Anemia	97%	97%	92%	79%
Febrile Neutropenia	90%	90%	88%	88%

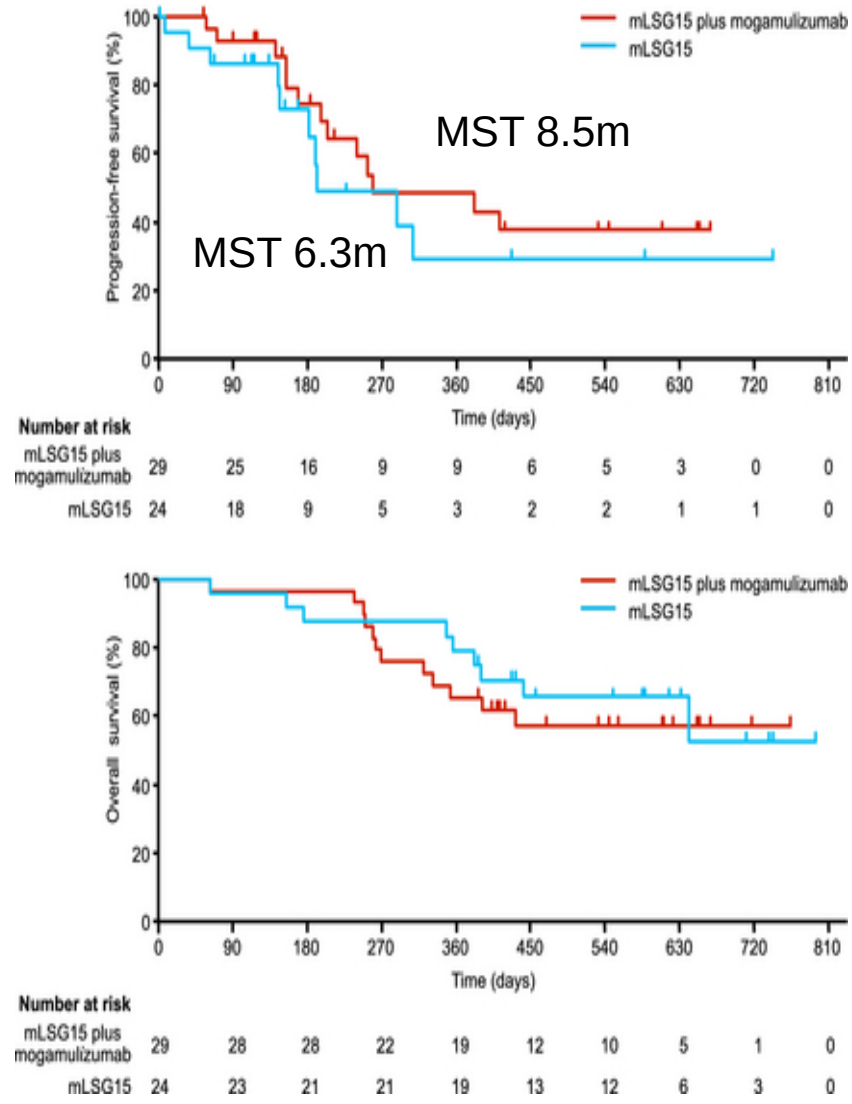
Treatment-related AEs with different frequency (≥10%)

AEs (CTCAEv4.0)	Patients affected, N			
	mLSG15 + Mogamulizumab (n=29)		mLSG15 (n=24)	
Preferred Term	All Grades	Grade ≥3	All Grades	Grade ≥3
Pyrexia	83%	10%	58%	0%
Papular rash	41%	21%	0%	0%
Erythematous rash	28%	7%	0%	0%
CMV infection	14%	0%	7%	0%
Intestinal lung disease	10%	0%	10%	0%

Ishida T, Tobinai K, et al. BJH 2015

Response and Survival
Chemo. alone vs. Chemo.+ mogamulizmab: a randomized phase II study

	mLSG15 + Mogamulizumab (n=29)	mLSG15 (n=24)
CR	9	5
CRu	6	3
PR	10	10
CR rate (95%CI)	52% (33-71)	33% (16-55)
ORR (95%CI)	86% (68-96)	75% (53-90)



Ishida T, Tobinai K, et al. BJH 2015

Phase I Dose-Escalation Study of Lenalidomide in Relapsed Patients with ATL or PTCL

Cohort	Patient ID	Age, years	Diagnosis	Number of Prior Treatments	Treatment Duration, days	Best Overall Response	TTR, days	DOR, days
Cohort 1	0021001	69	PTCL-NOS	1	21	PD		
	0011002	64	ATL-acute	2	637	PR	57	505
	0041003	69	ATL-unfavorable chronic	1	103	SD		
Cohort 2	0022001	42	PTCL-NOS	1	387	PR	106	282
	0032003	74	ATL-lymphoma	1	37	NA		
	0022004	61	ATL-acute	2	138	PR	55	92
	0042005	32	ALCL	11	56	PD		
	0032006	69	ATL-acute	1	66	PD		
	0022007	61	ATL-acute	2	> 28*	SD		
Cohort 3	0063001	71	ATL-acute	3	24	PD		
	0013002	53	PTCL-NOS	1	71	SD		
	0043003	60	ATL-unfavorable chronic	1	> 323*	PR	54	> 279*
	0053004	69	ATL-acute	1	25	PD		

Best Overall Response Rate : 31% (4/13, All patients), 33% (3/9, ATL patients)

Uike N, Tsukasaki K, Toninai K, et al. ASH 2012

Prevention and Treatment of HTLV-1-associated ATL

1st step: Prevention of HTLV-1 infection

Screening for HTLV-1 among blood donors

Refrain from breast feeding among carrier women

2nd step: Prevention of ATL development among HTLV-1 carriers

Risk factor for the development remains not fully elucidated

high viral load, etc.

No promising agents: anti- viral agents?, Mogamulizmab?

3rd step: Treatment of ATL

IFNa + AZT vs. Watchful waiting, or Mogamulizmab? for Indolent-ATL

allo-HSCT for aggressive ATL; RIST for aged patients

Mogamulizmab alone, or combined with chemo/HSCT or other new agents for agggressive ATL

new agents: HDACI, ImiDs, Folate, Purine analogs, Mo Abs

Grouping with other PTCLs; i.e. Brentuximab vedotin P3 trial

Acknowledgment: Mogamulizmab Study for ATL in Japan

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