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

Bologna
Royal Hotel Carlton
May 7-9, 2018

ATL
in
Mogamulizmab: a pan-T cell lymphoma drug

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T-Cell Lymphomas:
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finalization

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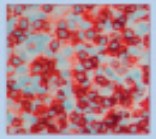

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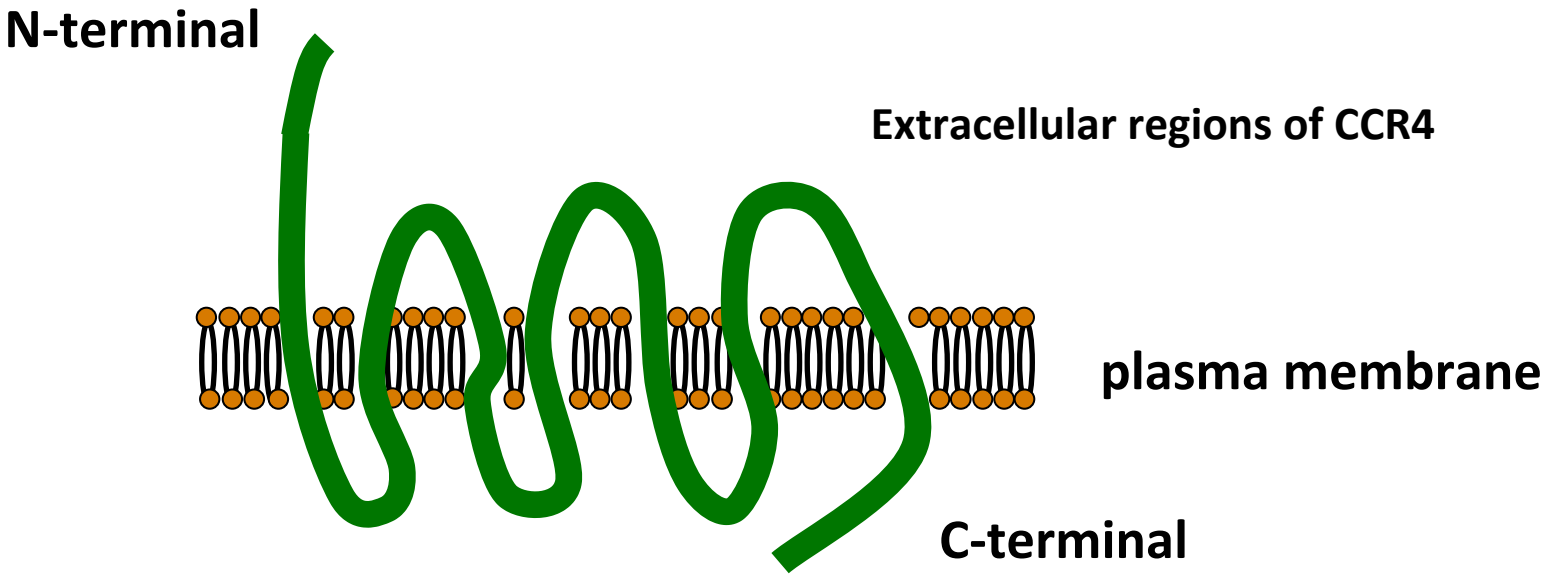
Disclosures of Kunihiro Tsukasaki

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			+			+	

CC chemokine receptor 4 (CCR4)



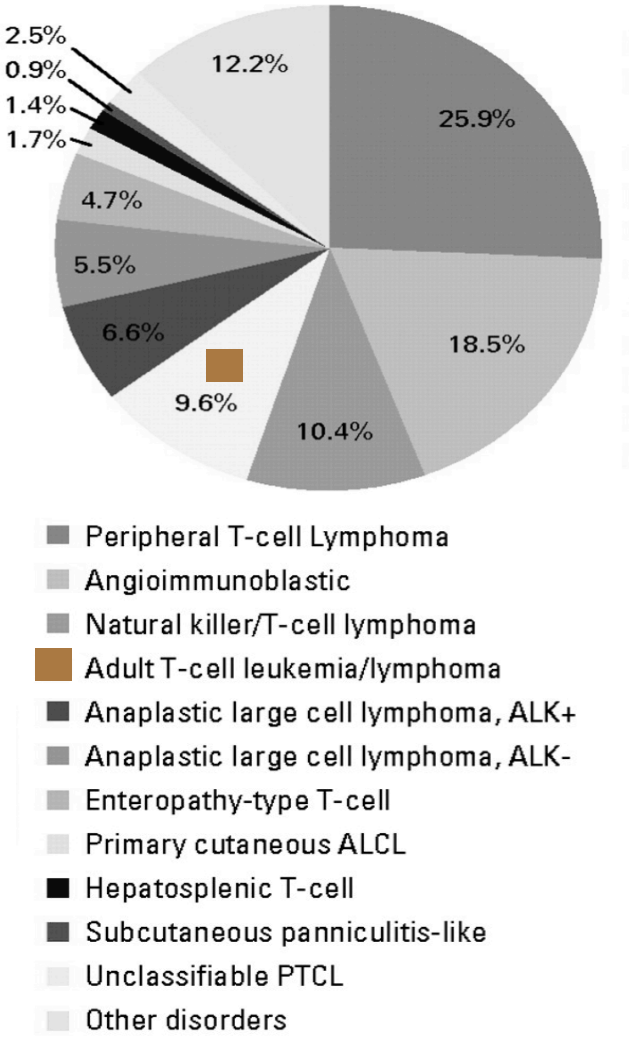
- The CCR4 gene is located on chromosome 3p24.
- CCR4 is a 7 transmembrane G protein-coupled receptor and consists of 360 aa.
- Expression in normal tissues: some of the T-lymphocytes (Th2/Treg cells) and plts.
- TARC/CCL17 and MDC/CCL22 are ligands of CCR4, associated with migration of T-cells to skin.
- Gain of function CCR4 mutation truncating cytoplasmic domain was detected in 29% of ATL.

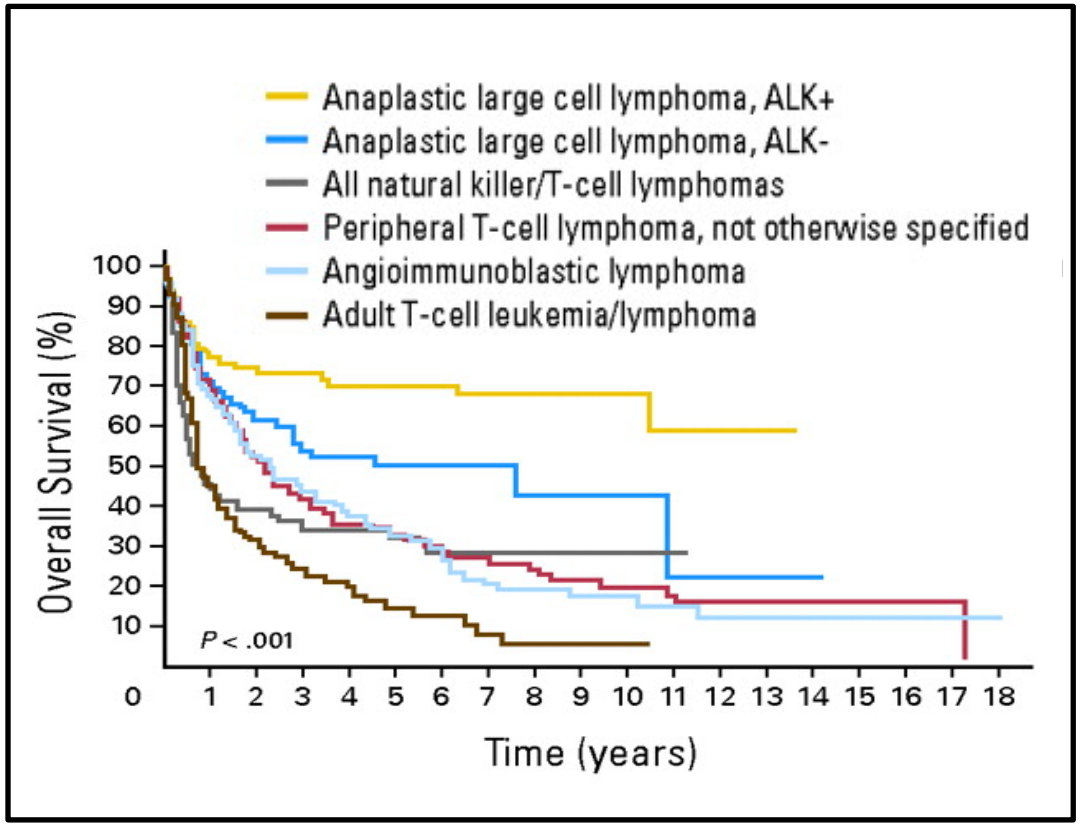
Expression of CCR4 in lymphoma

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

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

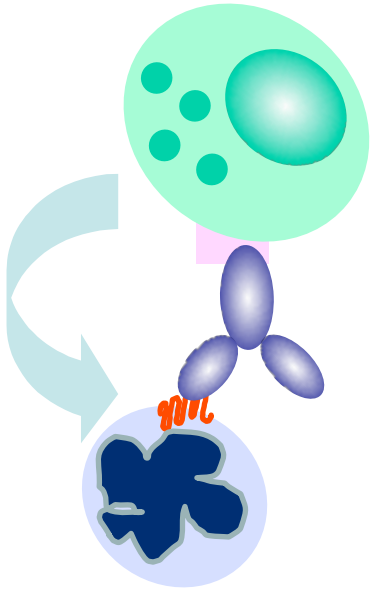
Concept

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

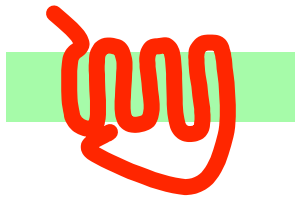
- **One of the most important functions of the therapeutic antibodies**
- **Development of a first-in-class zero-fucose humanized antibody with high ADCC activity targeting CCR4**



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)**



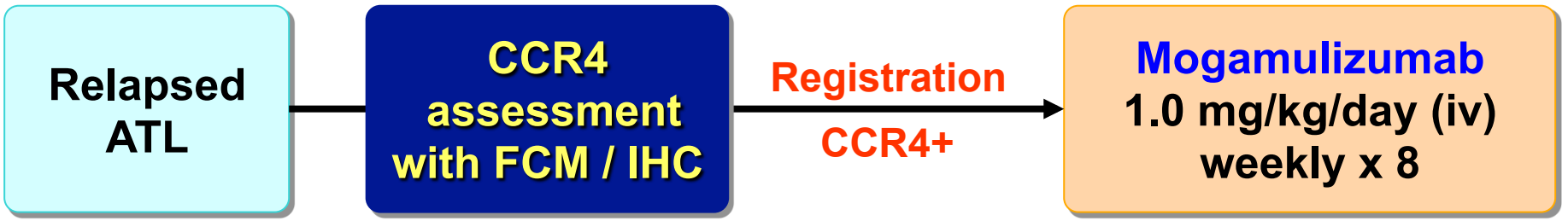
- **MTD was not reached until 1mg/kg in 16 pts.**
- **RR was 31% including 2 CRs among 13 ATL patients.**

→ Recommended phase II dose: 1.0 mg/kg

Yamamoto K, Tsukasaki K, Tobinai K et al. JCO 2

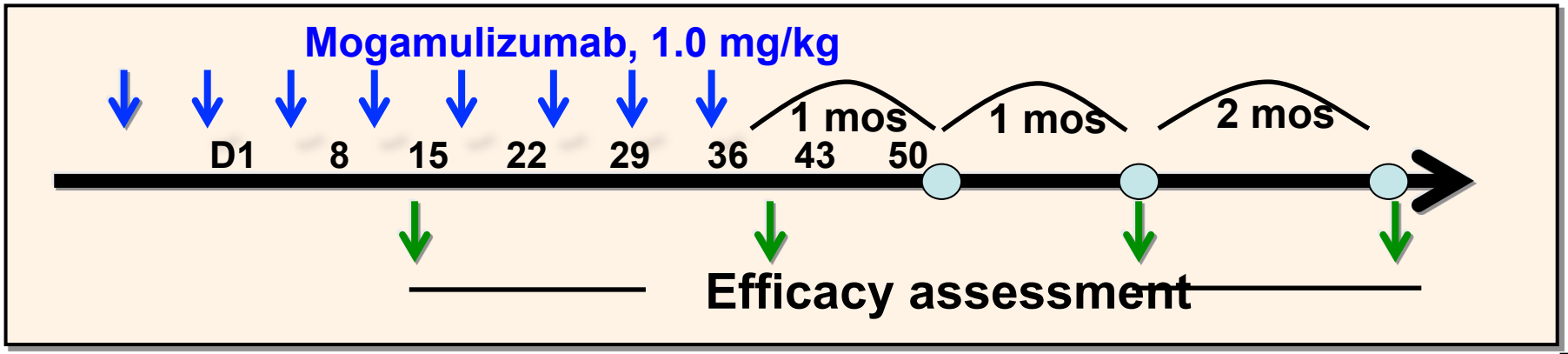
Phase II study of Mogamulizumab in relapsed ATL

A multicenter open labeled study



Primary endpoint; Overall response rate

Dosing and assessment schedule



Ishida T, Tsukasaki K, et al. JCO 2012

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, 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, et al. JCO 2012

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

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Overall	26	8	5	2	11	0	13	(50 %)	[30-70]

* 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, et al JCO 2007

Ishida T, Tsukasaki K, et al. JCO 2012

A prospective, multicenter, randomized study of anti-CCR4 monoclonal antibody mogamulizumab (moga) vs investigator's choice (IC) in the treatment of patients (pts) with relapsed/refractory (R/R) adult T-cell leukemia-lymphoma (ATL).

Adrienne Alise Phillips MD, MPH
Hematologic Malignancies-Lymphoma and Chronic Lymphocytic Leukemia

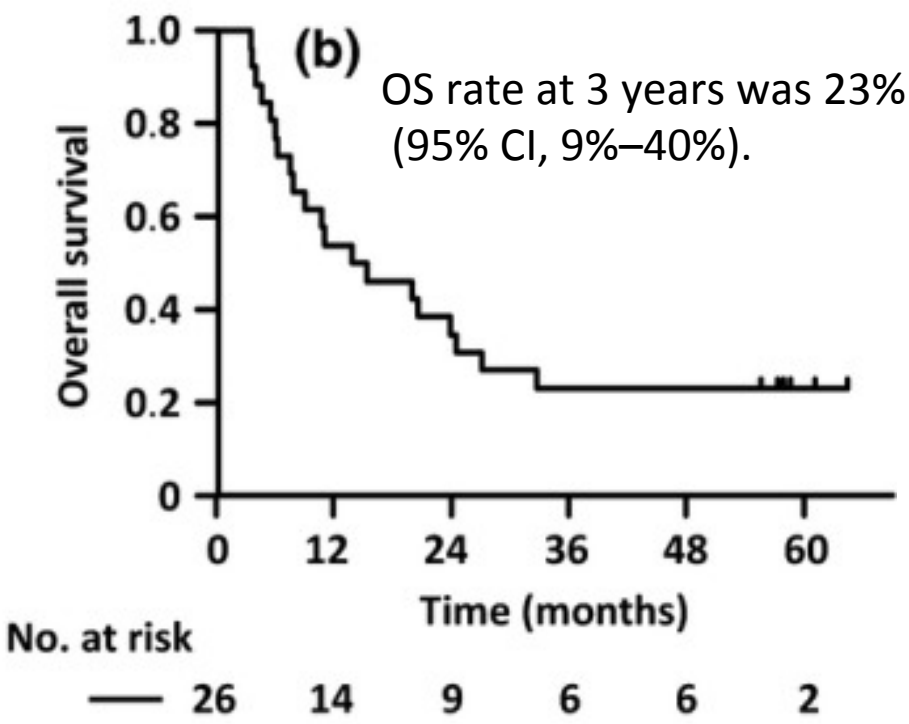
Results: Overall Response Rate

	Investigator's Choice* (N=24)	Mogamulizumab (N=47)
Investigator Assessment (IA)		
All Responses	0%	16 (34%)
Confirmed Responses	0%	7 (15%)
Independent Review (IR)		
All Responses	2 (8%)	13 (28%)+
Confirmed Responses	0%	5 (11%)

- Confirmed response = maintained at successive evaluations over approx. 8 weeks
- Median durations of confirmed response were 5.5 and 5 months for IA and IR, respectively
- 17% (3/18) of crossover patients had response with mogamulizumab
  - 1 confirmed response in crossover

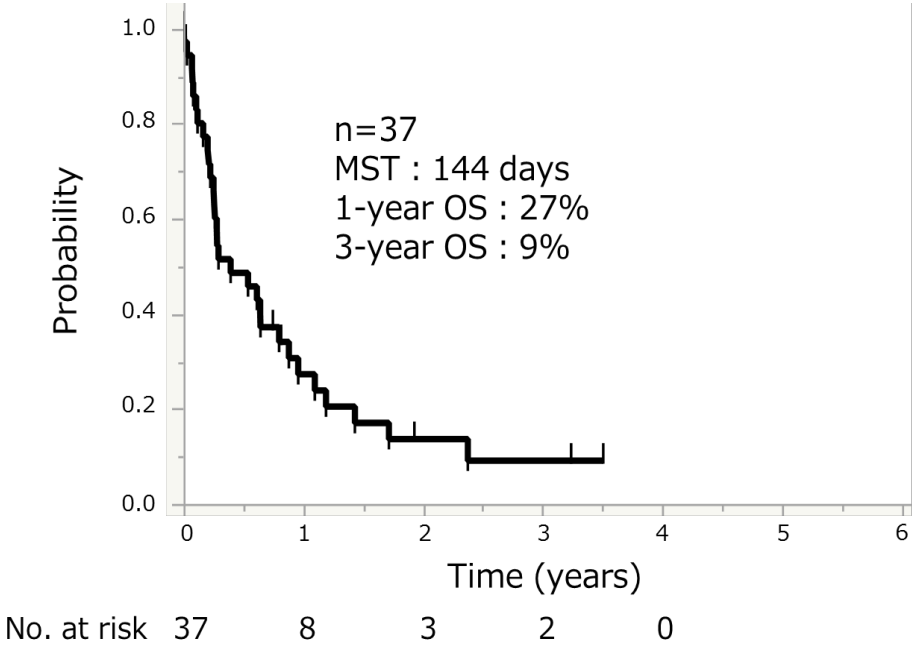
+ Updated from value of 23% reported in abstract
* Investigator's Choice: pralatrexate, DHAP, or gemcitabine/oxaliplatin

Follow-up of the P2 study of Mog in relapsed ATL in Japan



Ishida T, Imaizumi Y et al. Ca Sci, 2017

Post-approved survey of Mog in relapsed/refractory ATL in Japan



Imaizumi Y, Tsukasaki JK, et al. JSH, 2017

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)

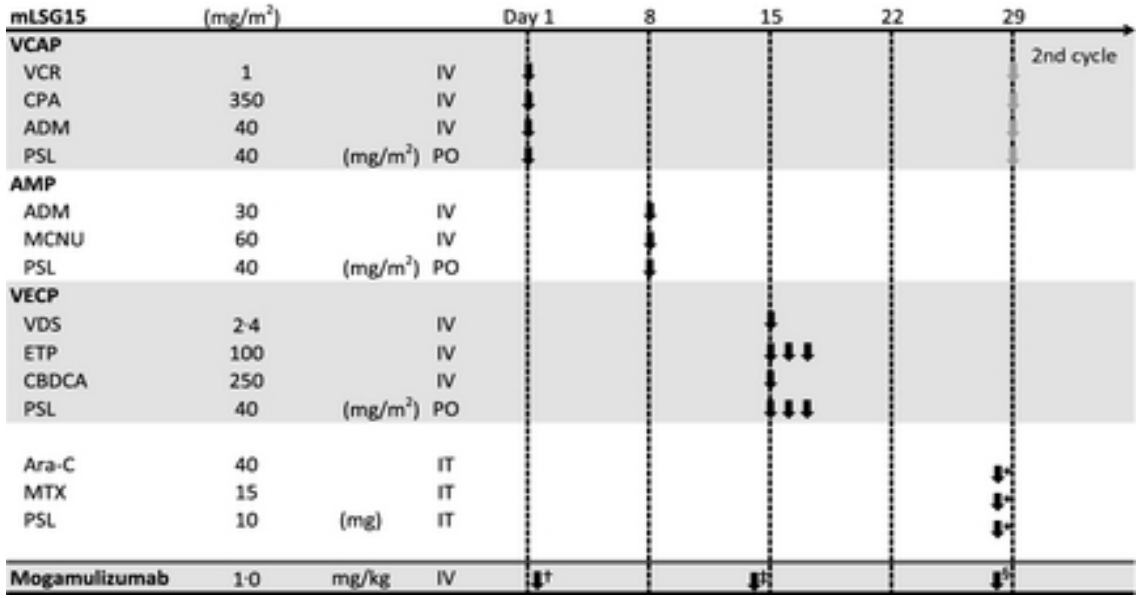
VCAP-AMP-VECP arm

(mLSG15×4cycles)

Open-label design

VCAP-AMP-VECP + Mogamulizumab arm

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



Primary end point;
%CR

Secondary end points;
ORR, PFS, OS, safty

Ishida T, 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, et al. BJH 2015

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

Most common treatment-related Hematological 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, et al. BJH 2015

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

Most common treatment-related Hematological 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%

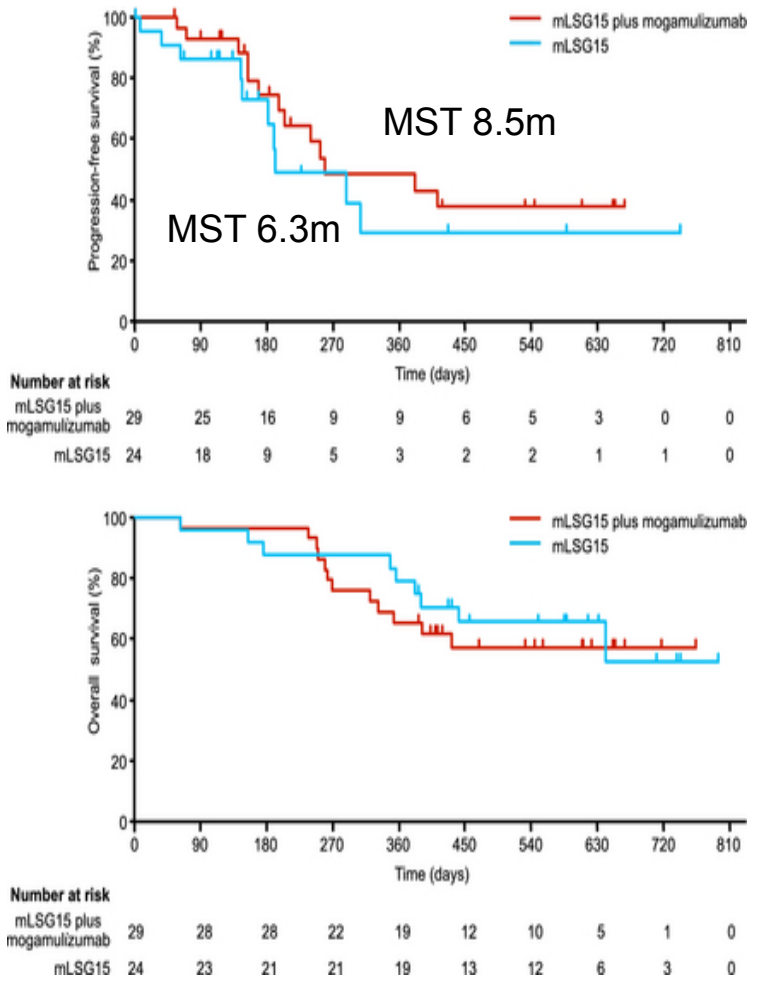
Treatment-related NH-AEs with different frequency (≥10%)

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%

Ishida T, et al. BJH 2015

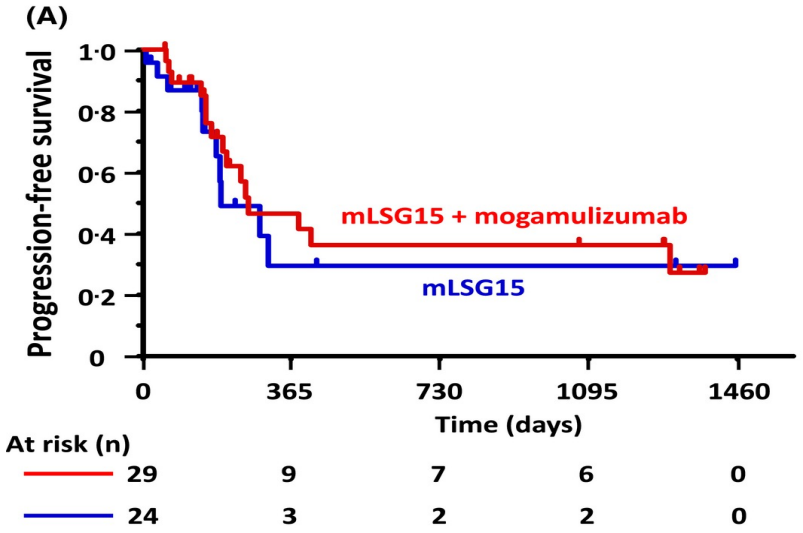
Response and Survival
Chemo. alone vs. Chemo.+ mogamulizmab: a randomized phase II study

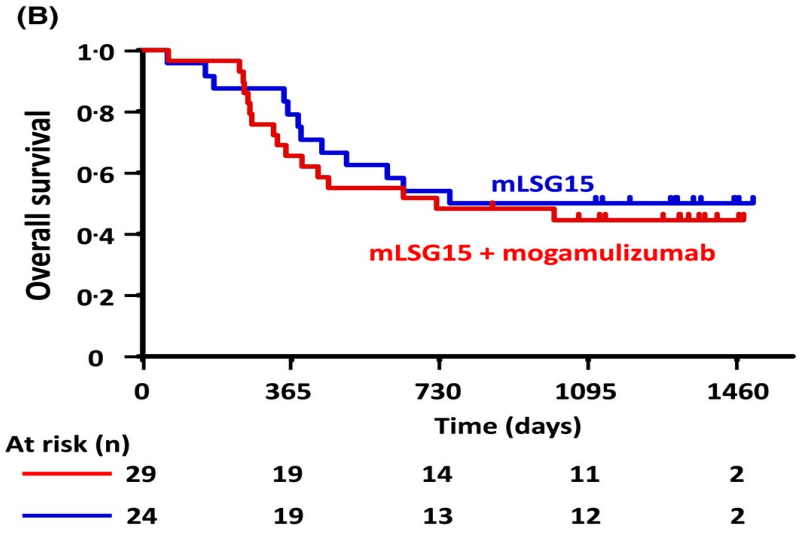
	mLSG15 + Mogamulizumab (n=29)	mLSG15 (n=24)
CR	9	5
CRu	6	3
PR	10	10
CR rate (95%CI)	52% (33-71)	33% (16-55)
ORR (95%CI)	86% (68-96)	75% (53-90)

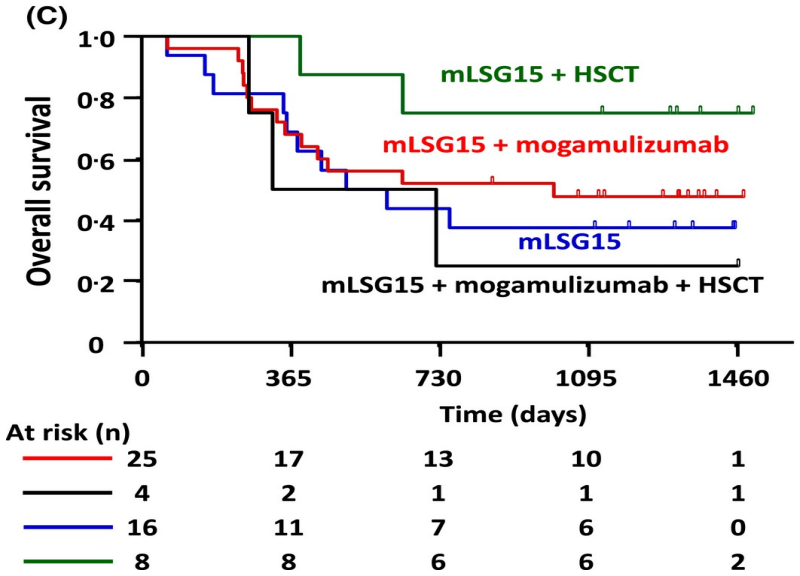


Ishida T, et al. BJH 2015

Follow-up of the randomized P2 study of chemo ± mogamulizmab in newly diagnosed aggressive ATL; impact on allo-HSCT



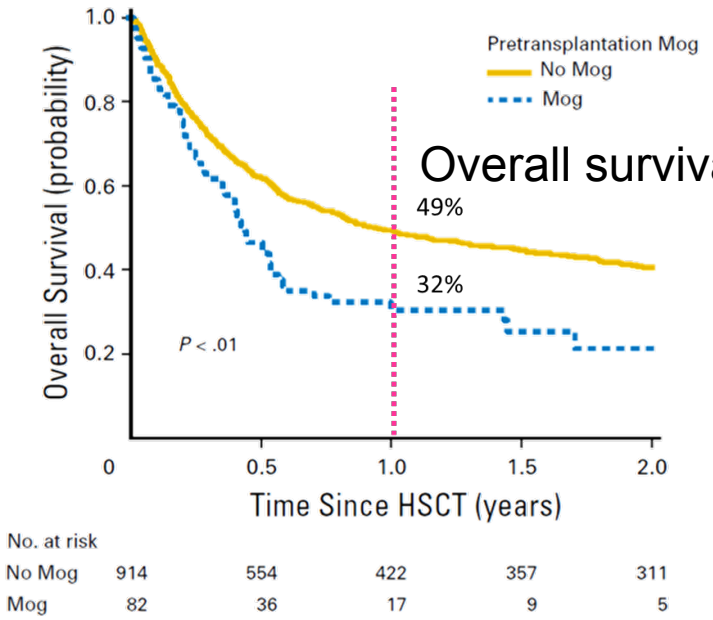


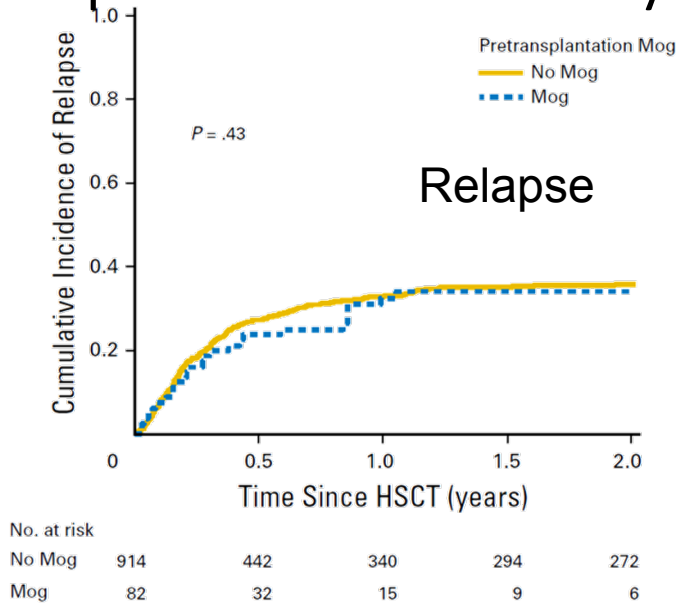


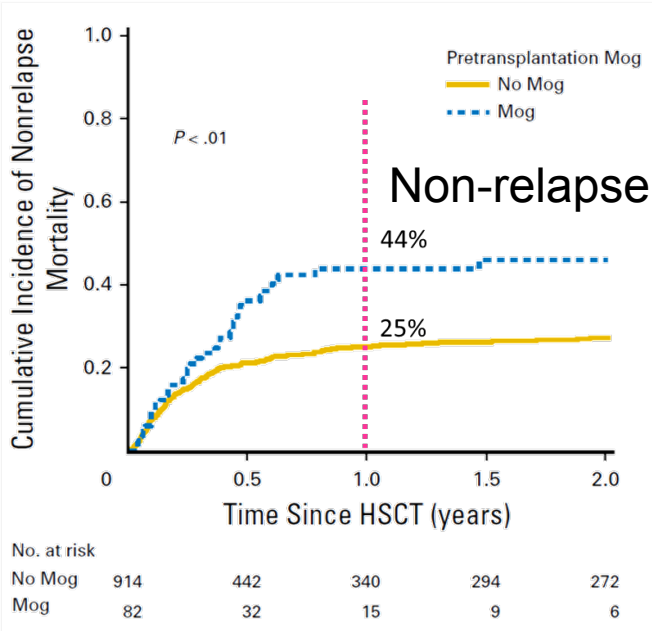
- No difference in survival between the arms possibly related to small sample size.
- Mog+chemo appears to be a feasible option for ATL pts ineligible for allo-HSCT.

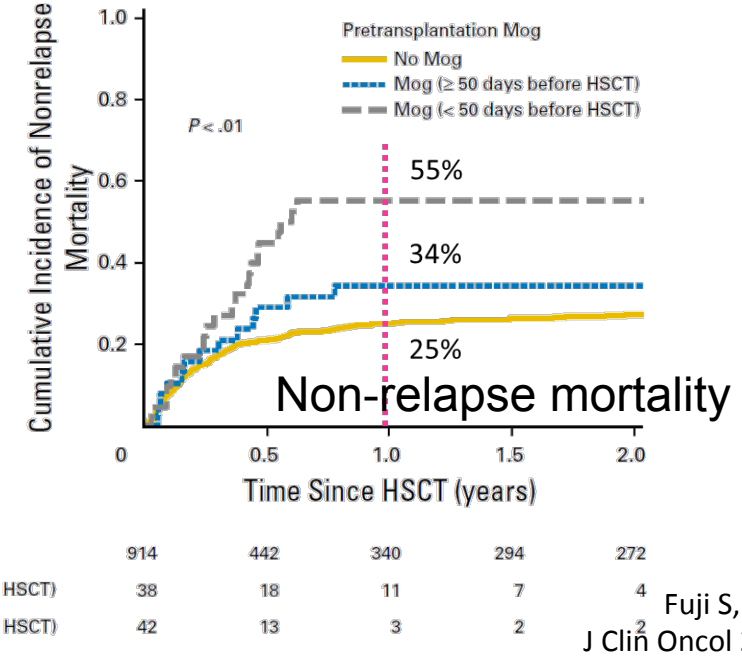
Ishida T, et al. BJH 2018

Pretransplantation Mogamulizumab Against ATL in nation-wide survey ; Severe GVHD, Non-relapse Mortality, and poor Overall Mortality









Fuji S, et al;
J Clin Oncol 2017.

Post-marketing all-case surveillance of mogamulizmab in pts with ATL (n=489) at 24sites for 14 months in Japan

- Adverse drug reactions (ADRs) were reported in 74% of patients, of which 36% were serious and 6% were fatal.
- Infusion reaction, skin disorder, infection, immune disorder, and tumor lysis syndrome were reported in 29, 34, 22, 4, and 3% of pts, respectively.
- Overall response rates were 57.5% in pts treated with mog alone (n=308), and 58.2% in pts treated with combination therapy (134).
- Response was associated with the number of Mog doses and the presence of skin eruption.

Ishitsuka T, et al. IJH 2017

Mogamulizmab in 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

Indolent-ATL

IFNa + AZT vs. Watchful waiting, or Mogamulizmab?

Aggressive ATL

Upfront allo-HSCT after intensive chemo for young pts

Mogamulizmab + chemo for allo-HSCT-ineligible pts

Mogamulizmab alone or combined with chemo or new agents such as lenalidomide as salvage therapy

Acknowledgment: Mogamulizmab Study for ATL in Japan

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