Mogamulizumab:
a defucosylated anti-CCR4 humanized monoclonal antibody
in PTCL

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Bologna, Royal Hotel Carlton
May 9, 2018

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

Bologna
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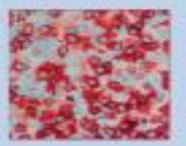
May 7-9, 2018



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Disclosures of Michinori Ogura MD, PhD

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
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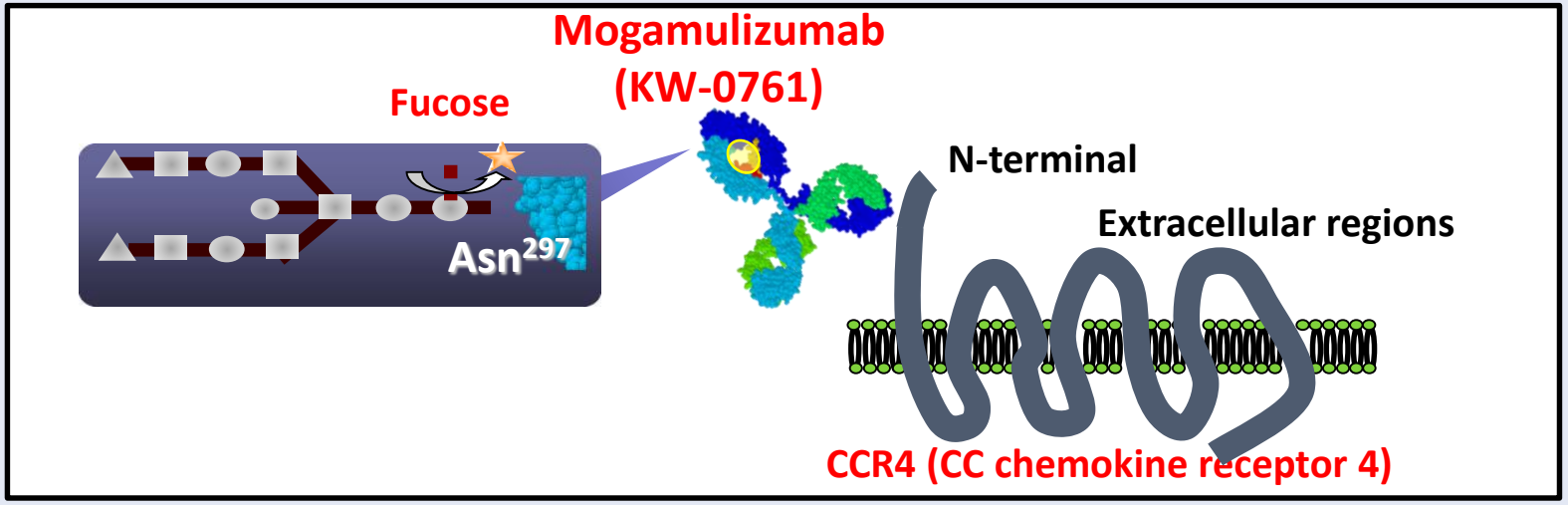
Celltrion	v					v	
Takeda					v		
Janssen Pharma					v		
Celgene					v	v	
AstraZeneka					v		
Mundipharma						v	
MeijiSeika Pharma						v	

Mogamulizumab (KW-0761)

- A first-in-class defucosylated humanized anti-CCR4 monoclonal antibody
- Highly potent antibody dependent cellular cytotoxicity (ADCC) activity
- No neutralizing activity, no complement dependent cytotoxicity (CDC) activity, no direct apoptosis induction
- Approved in Japan for treatment of relapsed/refractory ATL in 2012, and for relapsed/refractory PTCL in 2014

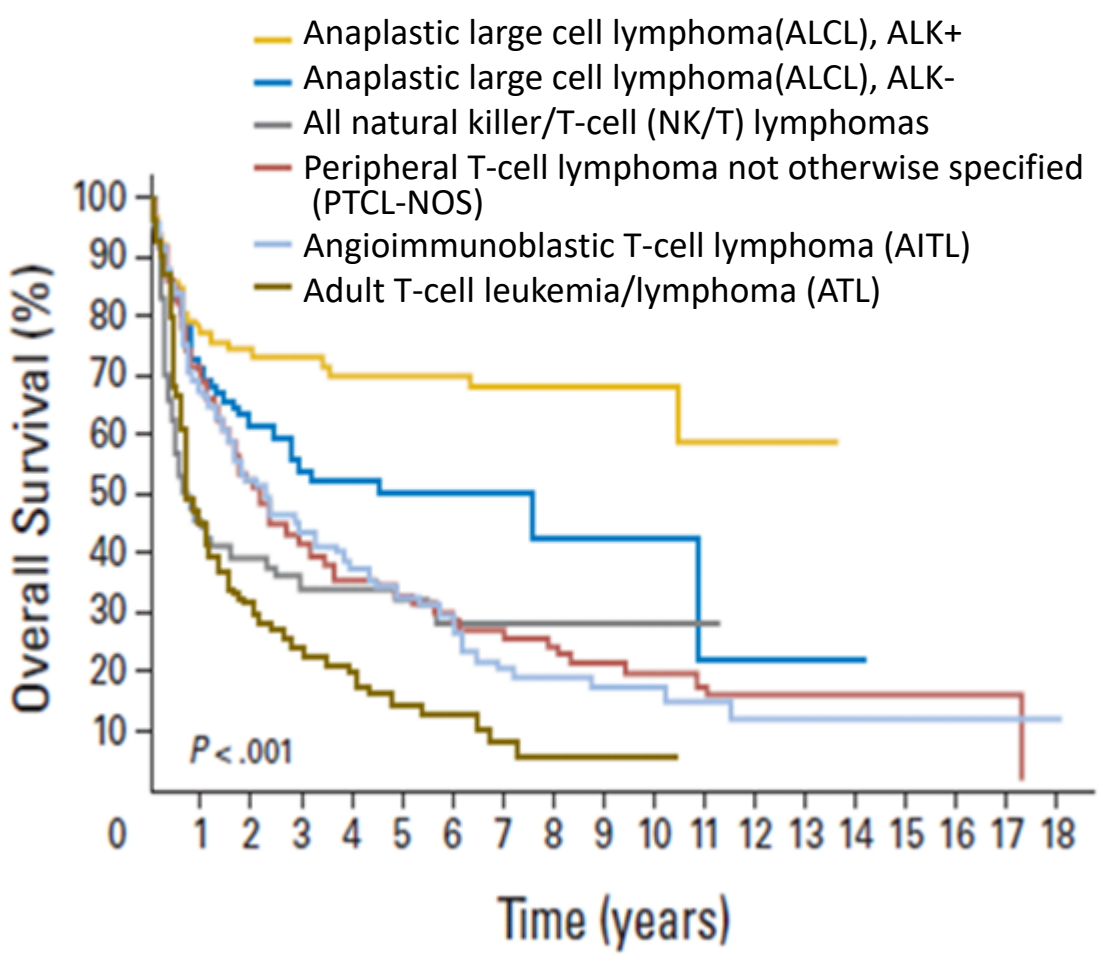


Shinkawa et al, J Biol Chem 2003;278:3466

Ishii et al, Clin Cancer Res 2010;16:1520

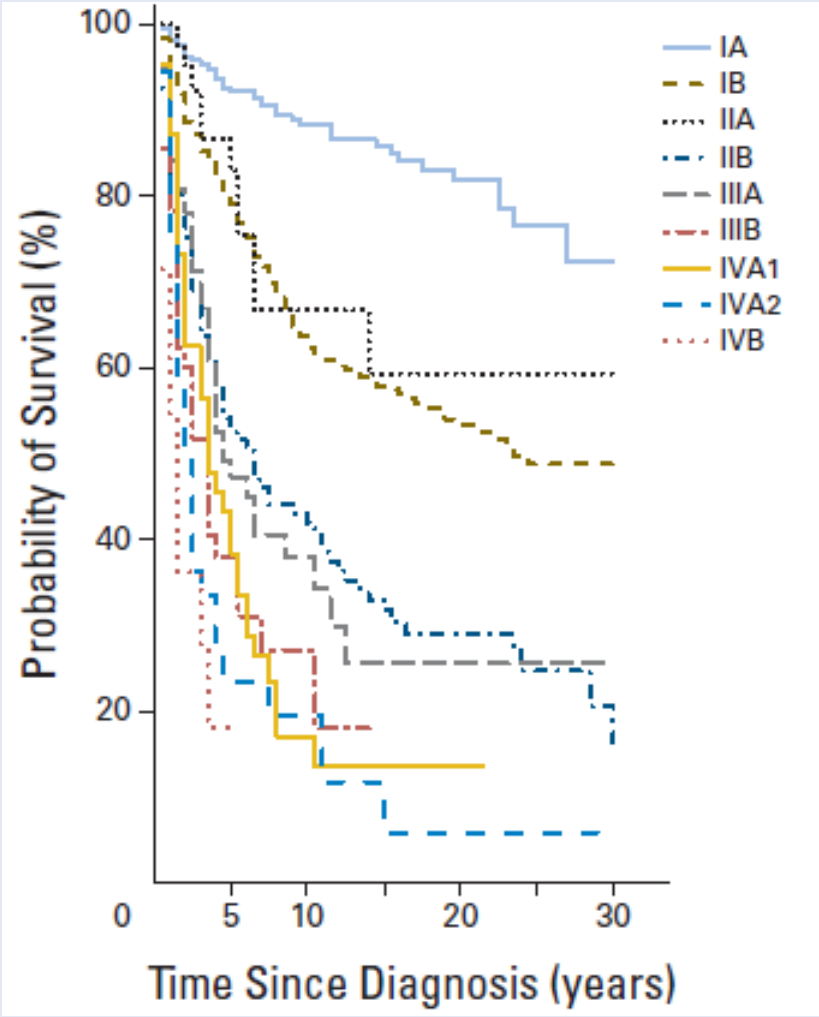
Peripheral / Cutaneous T-cell lymphoma

Peripheral T-cell lymphoma



International T-Cell Lymphoma Project ,
J Clin Oncol 2008; 26:4124

Mycosis Fungoides(MF)/Sézary Syndrome



Agar et al, J Clin Oncol 2010; 28:4730

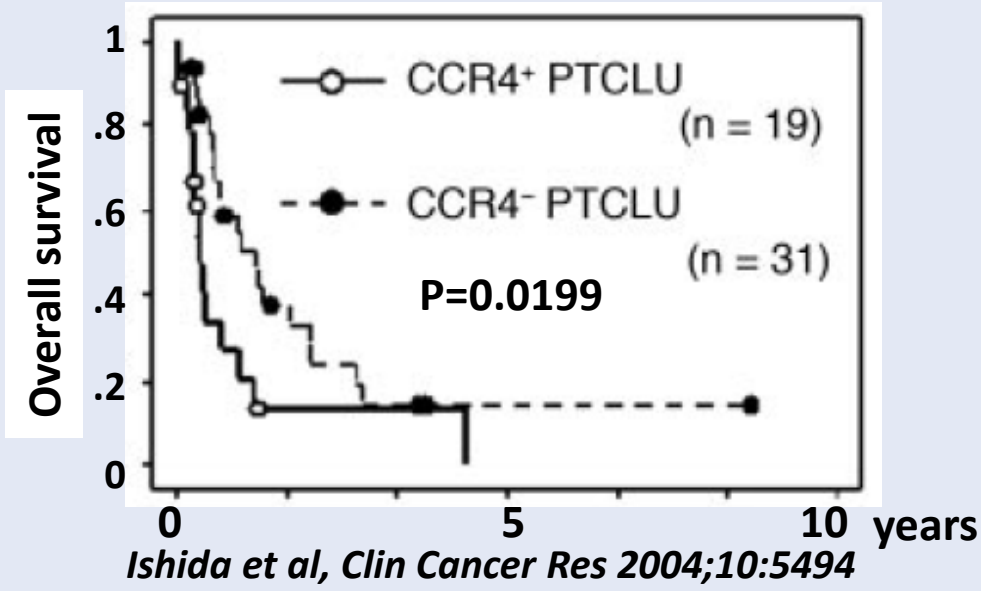
CCR4 expression and prognosis

Mature T-cell and NK-cell neoplasms

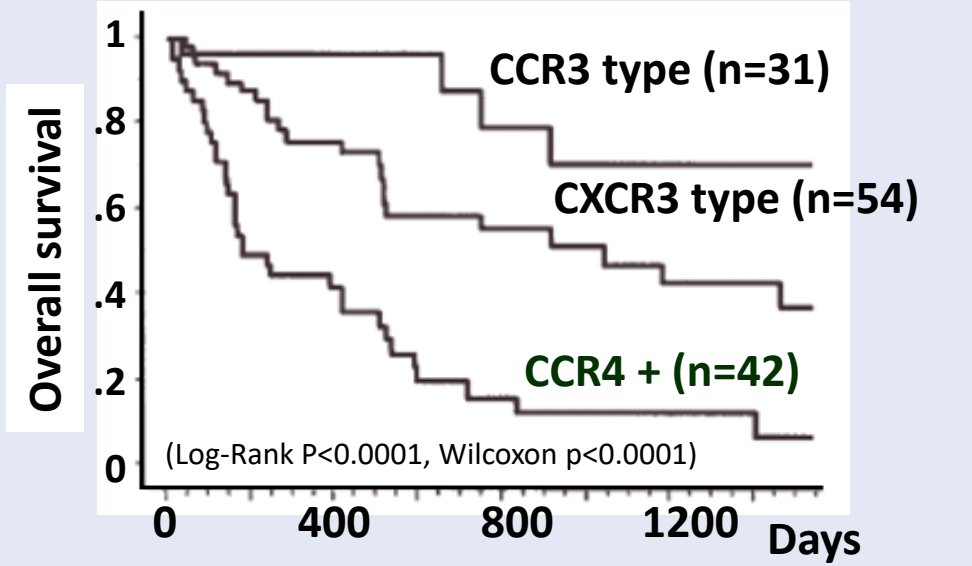
• NK/T, nasal type	1 /27	(3.7 %)
• MF in transformation	10 /20	(50.0 %)
• ALCL, ALK+	1 /24	(4.2 %)
• ALCL, ALK-	8 /16	(50.0 %)
• PTCL-NOS	24 /58	(41.3%)
• AITL	12 /38	(31.6 %)
• ATL	108 /120	(90.0 %)
• Others	5 /12	(41.6 %)

Ishida et al, Clin Cancer Res 2003;9:362
Ishida et al, Clin Cancer Res 2004;10:5494
Ishida et al, Int J Hematol 2005;82:148
Ishida et al, Leukemia 2006;20:2162
Yano et al, Clin Cancer Res 2007;13:6494

PTCL-NOS



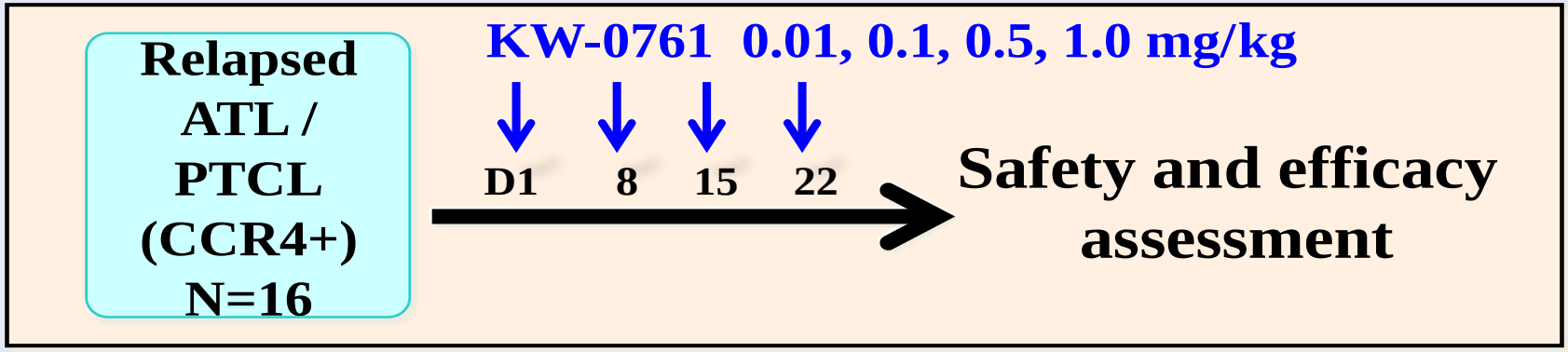
Ishida et al, Clin Cancer Res 2004;10:5494



Ohshima et al, Int J Oncol 2004;25:605 modified

Phase I Study of KW-0761 in Relapsed ATL/PTCL

A multicenter open labeled phase I dose-finding study in Japan

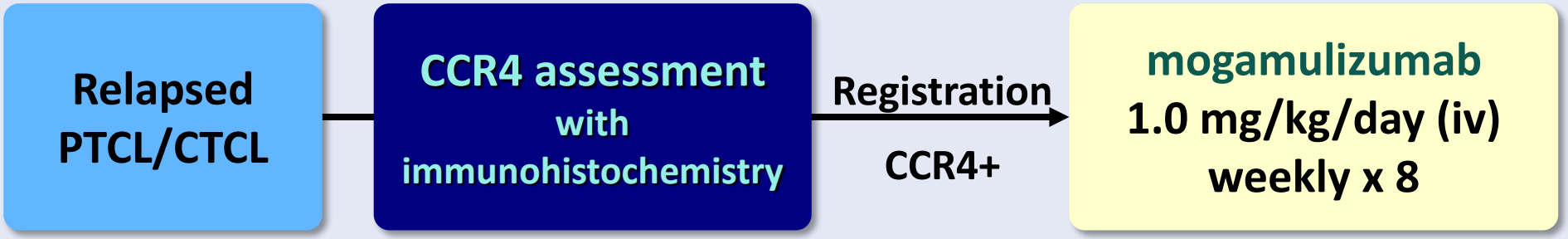


- One out of six patients @1 mg/kg cohort exhibited DLTs including G4 neutropenia, G3 febrile neutropenia and G3 rash.
- 44% (7/16) of ≥ G2 acute infusion reaction/cytokine release syndrome was observed and their reactions were tolerable.
- $T_{1/2}$ at 1.0 mg/kg after the 4^{th} dosing was 454 h± 164 h (18.9 ± 6.8 day).
- No anti-KW-0761 antibody
- Investigator-assessed responses for 16 enrolled patients (13 ATL, 2 PTCL-NOS, 1 MF): RR 31% (5/16 patients) including 3 CRs in ATL, and 2 PRs in ATL and PTCL-NOS.
- Recommended Phase 2 dose was defined to 1.0 mg/kg.

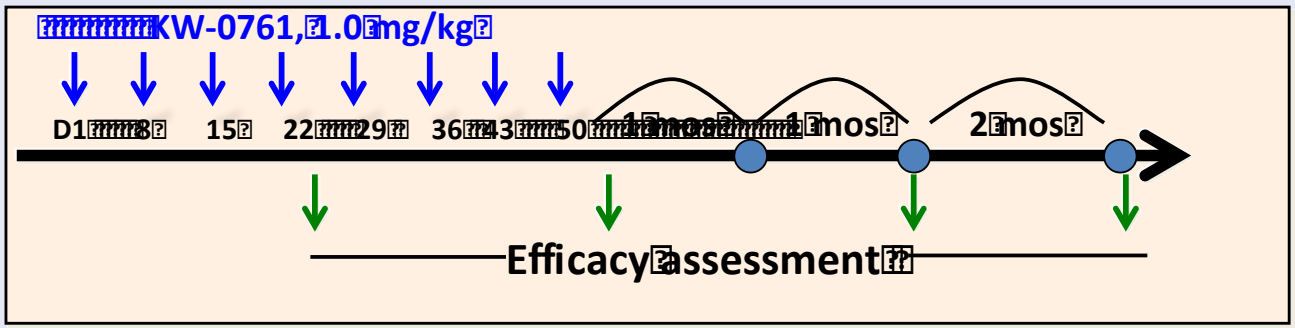
Yamamoto K, Ogura M, et al. J Clin Oncol. 2010;28:1591

Phase II study (0761-004) design

Multicenter open labeled study in Japan



Dosing and assessment schedule



- **Primary endpoint:**
  Best overall response rate (ORR)

- **Secondary endpoints:**
  Progression-free survival (PFS) , Overall survival (OS),
  Best response by disease lesion

-**Others:**
Adverse events, Anti-mogamulizumab antibody , Pharmacokinetics (PK)

Eligibility: Key inclusion and exclusion criteria

- ***CCR4-positive PTCL or CTCL**
- **Relapsed after the last chemotherapy**

  by which objective response was obtained

- PS**: 0 – 2
- Age≥ 20 years
- Normal function of the major organs

  (ex. LVEF, neutrophil and platelet count, and hemoglobin, AST, ALT, etc.)

- No prior allogeneic stem cell transplantation
- Negative for hepatitis B surface antigen and anti-hepatitis C virus antibody

*Subtypes were confirmed by a pathological review committee

**Eastern Cooperative Oncology Group (ECOG) performance status

Patient demographics and clinical characteristics (n=37*)

Characteristic		N	%
Age, years	Median (range)	64 (33-80)	
Sex	Male	23	62
	Female	14	38
PS	0	24	65
	1	12	32
	2	1	3
Number of Prior Chemotherapy	Median (range)	2 (1-6)	
Lymphoma Subtype			
	PTCL	29	78
	PTCL-NOS	16	43
	AITL	12	32
	ALCL-ALK(-)	1	3
	CTCL	8	22
	MF	7	19
	C-ALCL†	1	3

†Cutaneous anaplastic large cell lymphoma

*Among 38 patients enrolled, 37 received at least one infusion of mogamulizumab

Ogura M, et al. , JCO 2015, 32 : 1157

Efficacy assessment* (n=37)

Lymphoma Subtype	N	Best Response				ORR (%)	[95% CI]
		CR	PR	SD	PD		
PTCL	29	5	5	9	10	34	[18-54]
PTCL-NOS	16	1	2	6	7	19	
AITL	12	3	3	3	3	50	
ALCL ALK(-)	1	1 (CRu)	0	0	0	100	
CTCL	8	0	3	4	1	38	[9-76]
MF	7	0	2	4	1	29	
C-ALCL	1	0	1	0	0	100	
Total	37	5	8	13	11	35	[20-53]

*Evaluated by Efficacy Assessment Committee

Ogura M, et al. , JCO 2015, 32 : 1157

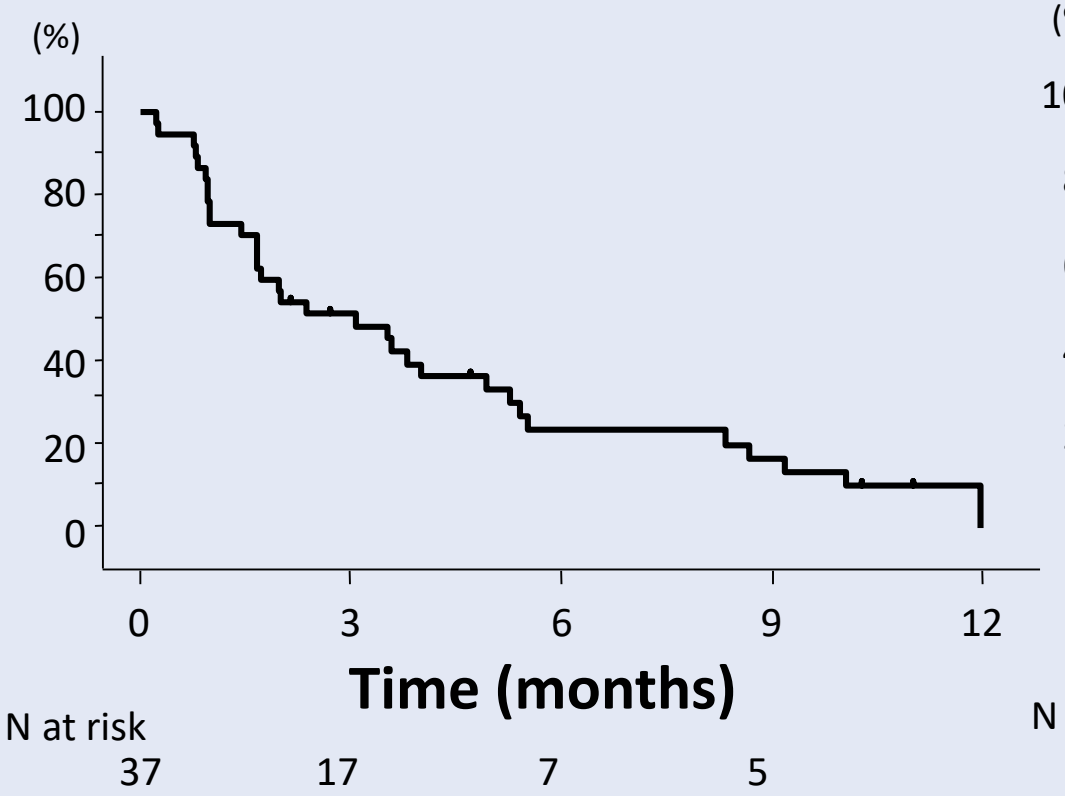
Response by disease site/CCR4/prior therapy

	N	Best Response				ORR (%)
		CR	PR	SD	PD	
Total	37	5 (1CRu)	8	13	11	35
Disease Site						
Lymph nodes	33	7	4	12	10	33
Skin	12	1	6	3	2	58
Peripheral Blood	1	0	1	0	0	100
CCR4 Expression						
1+	6	1	1	3	1	33
2+	6	1	2	2	1	50
3+	25	3 (1CRu)	5	8	9	32
Prior Chemotherapy						
1-2	29	4	4	12	9	28
3<	8	1 (CRu)	4	1	2	63

Ogura M, et al. , JCO 2015, 32 : 1157

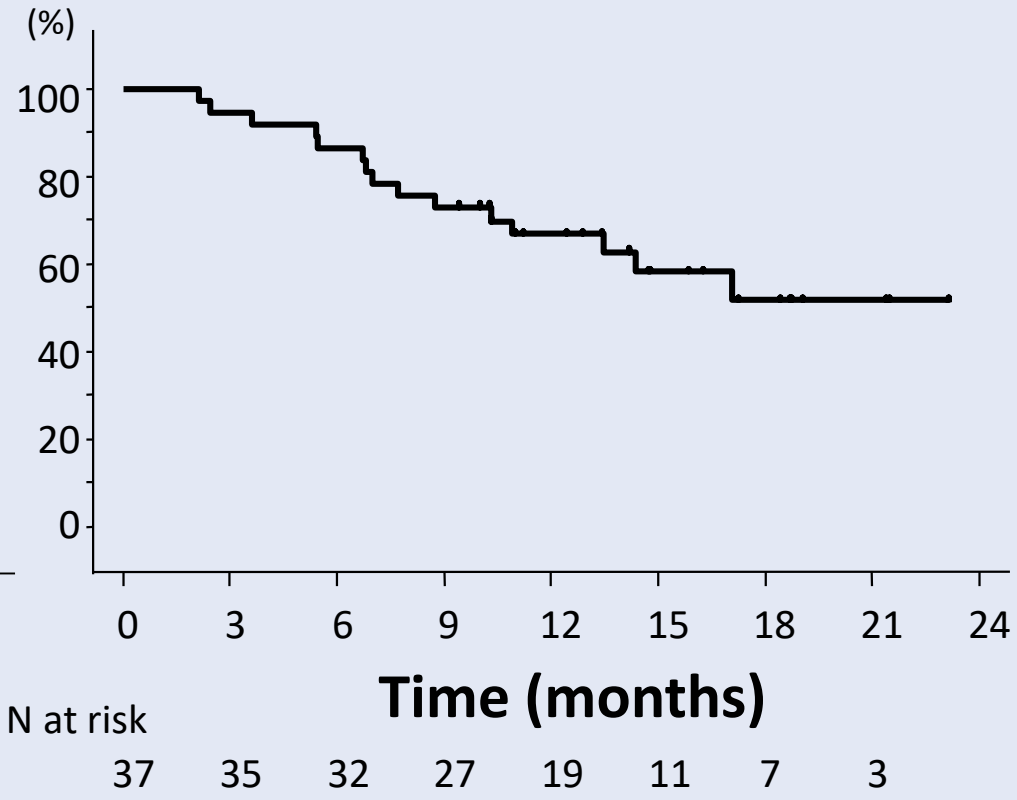
Progression-free survival (PFS)

	Median PFS (months)	[95%CI]
Total	3.0	[1.6-4.9]



Overall survival (OS)

	Median OS (months)	[95%CI]
Total	(Not reached)	[10.7-not estimated]



Ogura M, et al. , JCO 2015, 32 : 1157

Adverse events* (n=37)

*Possibly/probably/definitely drug-related

Non-Hematologic AEs	Patients affected, N			
	Grade		All Grades	
	3	4		
Pyrexia	0	0	11	30%
ALP increased	1	0	8	22%
ALT increased	1	0	8	22%
Phosphorus decreased	1	0	6	16%
Hypokalemia	1	0	2	5%
Secondary malignancy †	0	1	1	3%
Herpes oesophagitis	1	0	1	3%
Infection	1	0	1	3%
Oral candidiasis	1	0	1	3%
Pneumonia	1	0	1	3%
Polymyositis	1	0	1	3%
Skin disorders	4	0	19	51%
Acute Infusion reaction	0	0	9	24%

† Diffuse large B-cell lymphoma

Hematologic AEs	Patients affected, N			
	Grade		All Grades	
	3	4		
Lymphopenia	16	11 (30%)	30	81%
Leukocytopenia	3	2 (5%)	16	43%
Neutropenia	4	3 (8%)	14	38%
Thrombocytopenia	0	1	14	38%
Anemia	1	1	5	14%
Febrile Neutropenia	1	0	1	3%

Another phase II study for relapsed ATL, skin disorders were observed in 67% (18/27) patients.

Fifteen severe adverse events were observed in 8 patients.

Ogura M, et al. , JCO 2015, 32 : 1157

Conclusions

- All of 37 pts received 1. 0 mg/kg of mogamulizumab were evaluable for efficacy analysis.
- 35% of ORR (13/37; 95% CI, 20% - 53%) met the primary endpoint defined as the best ORR .
- Median PFS was 3.0 months and median OS has not yet reached.
- Most common adverse events were skin disorders, acute infusion reaction, pyrexia and hematologic toxicities.
- Grade 3 rash was observed in 4 pts. However, they were recovered or recovering by steroid-treatments.

Mogamulizumab is an effective agent with acceptable toxicity profiles for pts with relapsed PTCL and CTCL.

Acknowledgments

Investigators

Katsuya Fujimoto
Kenichi Ishizawa
Kensei Tobinai
Kiyohiko Hatake
Kiyoshi Ando
Michinori Ogura
Kazuhito Yamamoto
Takashi Ishida
Motoko Yamaguchi
Masafumi Taniwaki
Mitsune Tanimoto
Toshihiro Miyamoto
Naokuni Uike
Kunihiro Tsukasaki
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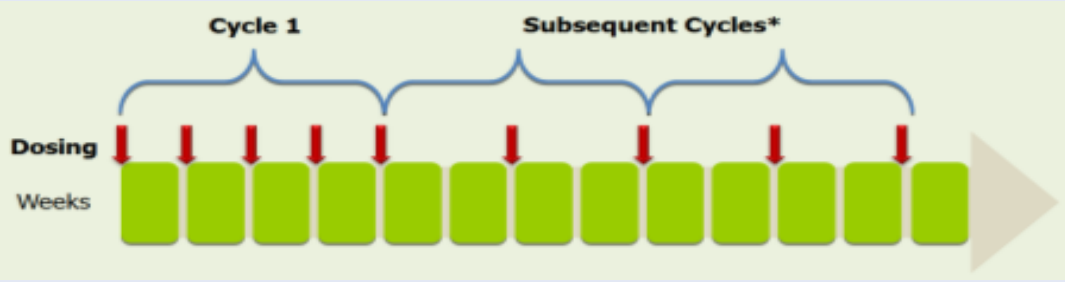
Sponsored by

KYOWA KIRIN

We would like to thank the patients who participated in this study and their families, as well as the research nurses, study coordinators, and operations staff.

Phase II Study of KW-0761 in CCR4 + r/r PTCL in EU

Zinzani PL, et al., Haematologica. 2016;101:e407-e410.



- **Mogamulizumab dosing**
  - 1.0 mg/kg, iv
  - Day 1, 8, 15, 22 of cycle 1
  - Day 1 and 15 of subsequent cycles
  - Until PD or study withdrawal.

Overall Response by Histological Subtype

Best Overall Response by Histological Subtype	Number of Subjects	CR/PR N (%)	SD N (%)	≥SD N (%)
PTCL-NOS	15	2[a] (13%)	6 (40%)	8 (53%)
AITL	12	2 (17%)	3 (25%)	5 (42%)
TMF	3	0	1 (33%)	1 (33%)
ALCL-ALK neg	4	0	2 (50%)	2 (50%)
ALCL-ALK pos	1	0	0	0
Efficacy Evaluable Subjects	35	4 (11%)	12 (34%)	16 (46%)

a: One patient had CR by CT scan but did not have bone marrow done for confirmation of CR.

[N.B.: 3 subjects did not have post-baseline assessment for efficacy]

TMF; transformed mycosis fungoides

Comparison of Phase II studies in Japan and EU

	P-2 in Japan	P-2 in EU
PS 2	0.4%(1/37) *	39%(15/38)
Median No. of previous systemic therapy	2 (1-6)	2 (1-8)
Refractory to last systemic therapy	0% (not eligible)	45% (17/38)
Schedule of Moga* administration	1 mg/week x 8 weeks	1mg/week x 4 weeks 1 mg/ 2 weeks from 5th dose until PD
Median No. of administered Moga*	8	6

* Moga: mogamulizumab

Summary

- **Mogamulizumab is an effective agent with acceptable toxicity profiles for patients with relapsed PTCL and CTCL in Japanese phase II study, and approved in patients with relapsed/refractory PTCL/CTCL in Japan.**
- **However,**
  - **Refractory patients were not included.**
  - **Sample size is small.**
  - **No randomized study**
  - **Although the reason is unclear, the efficacy was lower in a phase II study in EU against patients with relapsed/refractory PTCL.**
- **A large scaled randomized study will be needed.**

Possible Future Directions

- **Combination of mogamulizumab with lenalidomide in PTCL**
  - **ORR by lenalidomide; 22% (12/54) in relapsed/refractory PTCL including 11% CR/CRu; 31% in relapsed/refractory AITL including 15% CR/CRu. *Morschhauser F, et al., Eur J Cancer. 2013;49:2869-76.***
- **Combination of mogamulizumab with PD-1/PD-L1 blockade in PTCL**
  - **CCR4 is expressed on CD45RA-FOX3highCD4+ effector regulatory T (Treg) cells**
  - **Treg cells involved in the tumor escape from host immunity in the tumor microenviroenment**
  - **B7-H1 (PD-L1, CD274) was expressed by tumor cells, monocytes, and monocyte-derived cells within the tumor microenvironment in PTCL and was found to inhibit T-cell proliferation and promote the induction of FoxP3(+) regulatory T cells. *Wilcox RA, et al., Blood. 2009; 114:2149-58.***
- **Sequential use of mogamulizumab followed by HDAC inhibitors in PTCL**
  - **Histone deacetylase inhibitors downregulate CCR4 expression and decrease mogamulizumab efficacy in CCR4-positive mature T-cell lymphomas. *Kitadate A, et al., Haematologica. 2018;103:126-135.***
- **etc**

Thank you for your attention