New Drugs in Hematology

Mogamulizumab, a defucosylated anti-CCR4 humanized monoclonal antibody, in ATL, PTCL and CTCL

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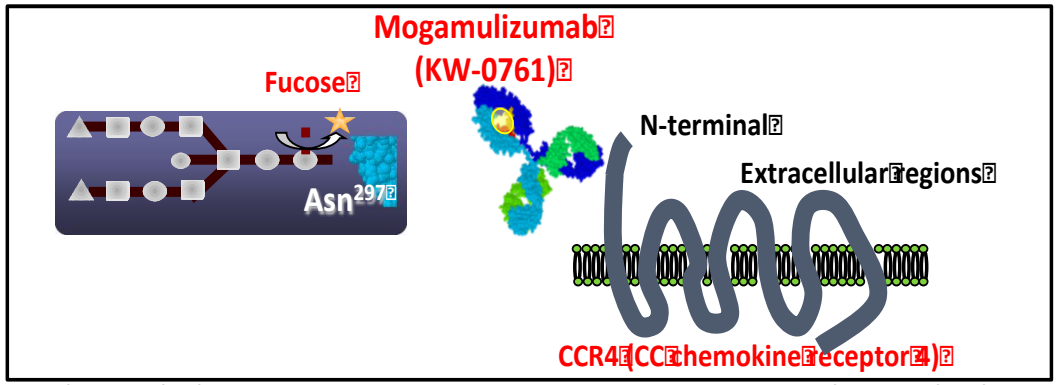
Disclosures of Michinori Ogura MD, PhD

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
SymBio	v						
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
- CCR4 is G protein-coupled receptor for macrophage-derived chemikine and thymus(MDC) and activation–regulated chemokine (TARC)
- CCR4 is over-expressed in ATL, PTCL and CTCL
- Approved in Japan for treatment of relapsed/refractory CCR4+ ATL or CTCL in 2012, for CCR4+ relapsed/refractory PTCL in 2014 and for relapsed/refractory CTCL without relation to CCR4 positivity in 2018



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

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

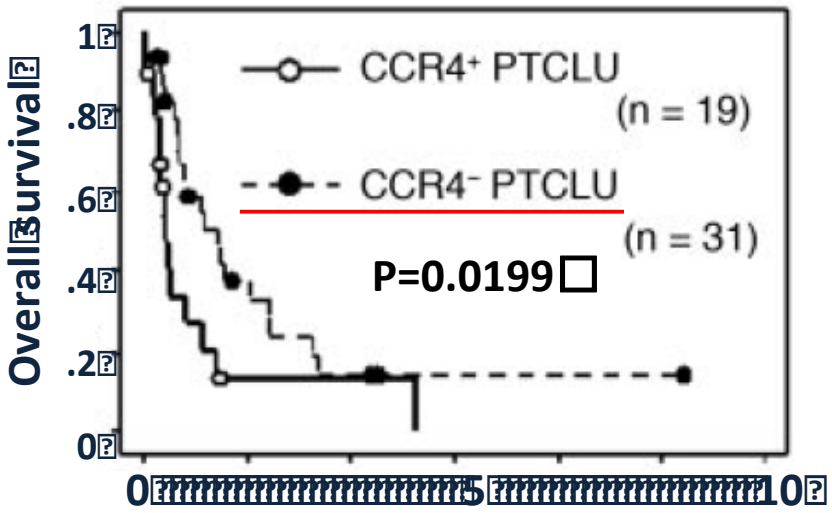
CCR4 expression and prognosis of PTCL/CTCL

Mature T-cell and NK-cell neoplasms

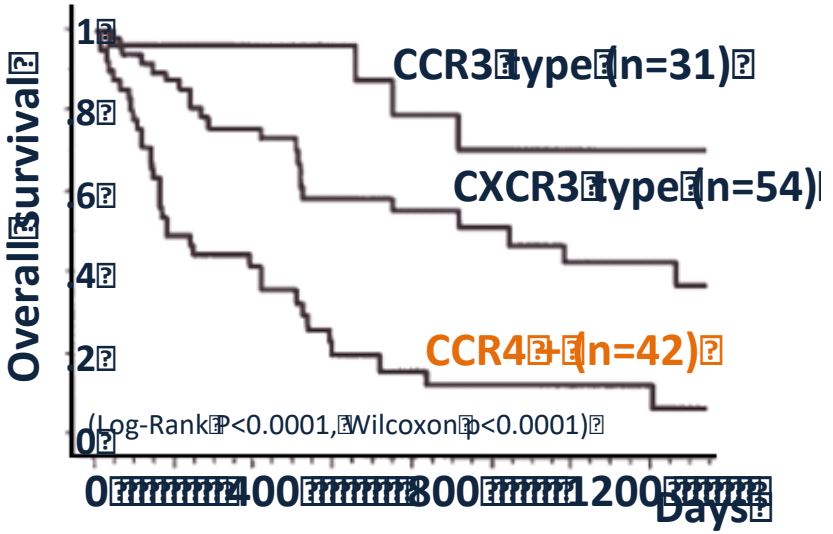
- NK/T, nasal type 1/27 (3.7%)
- MF in transformation 10/20 (50.0%)
- ALCL, ALK+ 1/24 (4.2%)
- ALCL, ALK- 8/16 (50.0%)
- PTCL-NOS 24/58 (41.3%)
- AITL 12/38 (31.6%)
- ATL 108/120 (90.0%)
- Others 5/12 (41.6%)

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



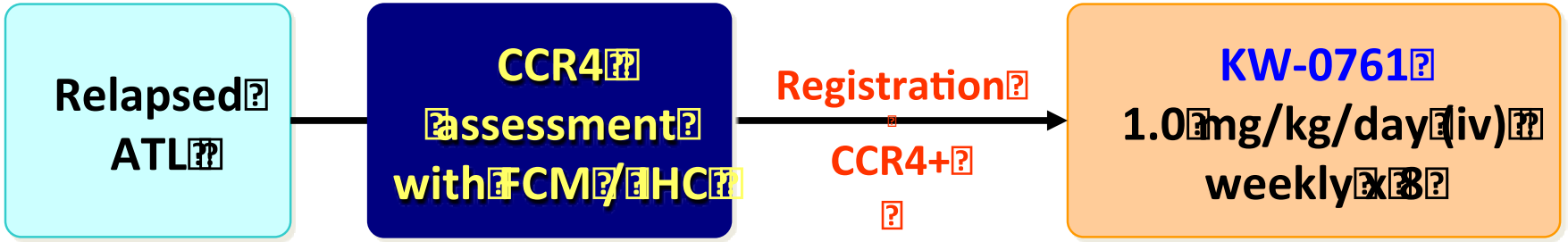
Ishida et al, Clin Cancer Res 2004;10:5494



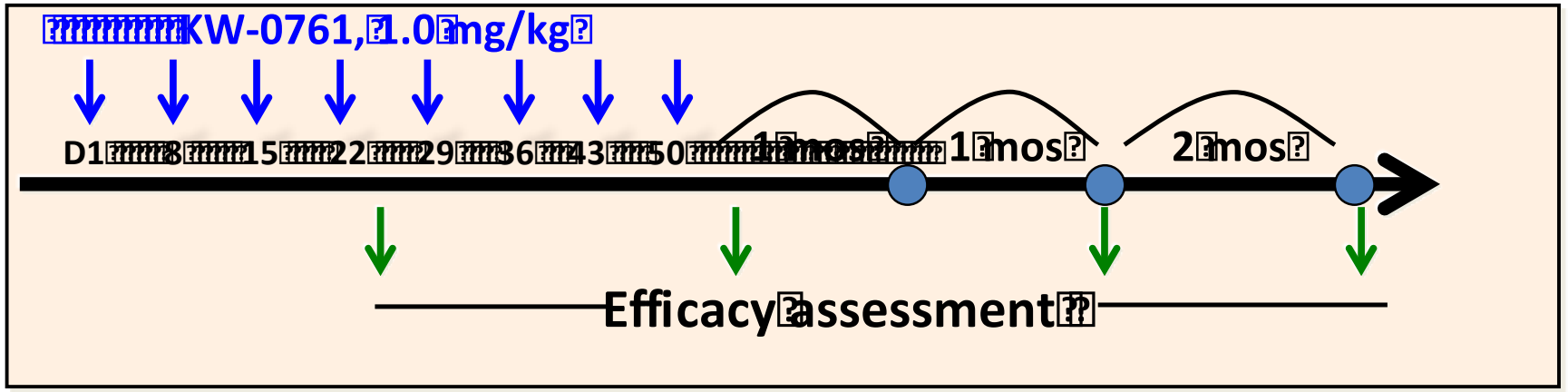
Ohshima et al, Int J Oncol 2004;25:605 modified

Phase II Study of KW-0761 in Relapsed ATL
(0761-002 Pivotal Phase II Study)

A multicenter, single-arm, open-label study



Dosing and assessment schedule



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

Ishida T, Ogura M, et al. J Clin Oncol. 2012;30:837

Efficacy Assessment* (n=26**) (0761-002 Phase II study)

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 (31%)**	**5 (19%)**	2	11	0	**13 (50)**	[30-70]

*According to the 2009 criteria (Tsukasaki, et al. *J Clin Oncol 2009;27:453*)

**One pt with concurrent colon cancer was excluded

***Includes CRu

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

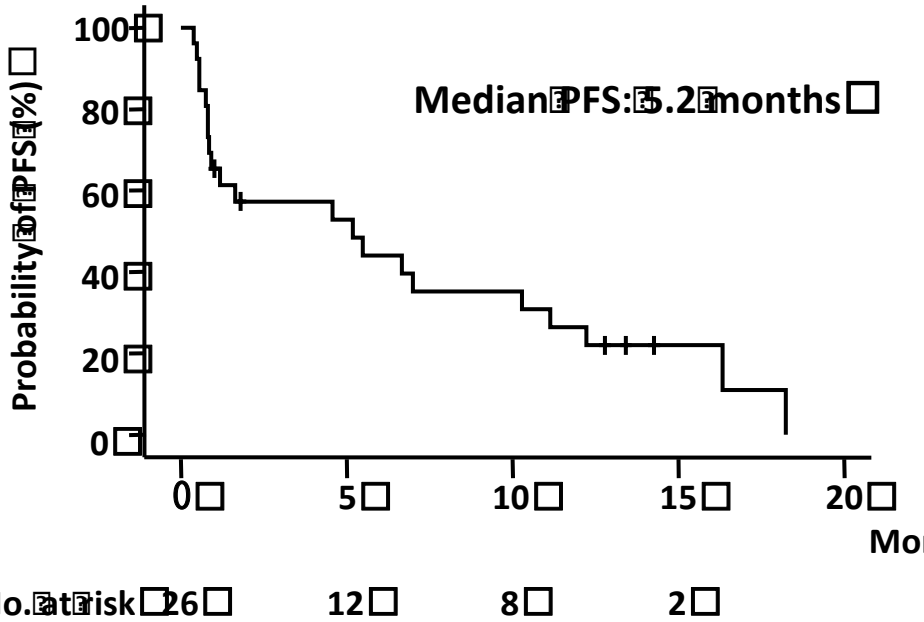
(Lower limit of the 95%CI > 35%)

Ishida T, Ogura M, et al. J Clin Oncol. 2012;30:837

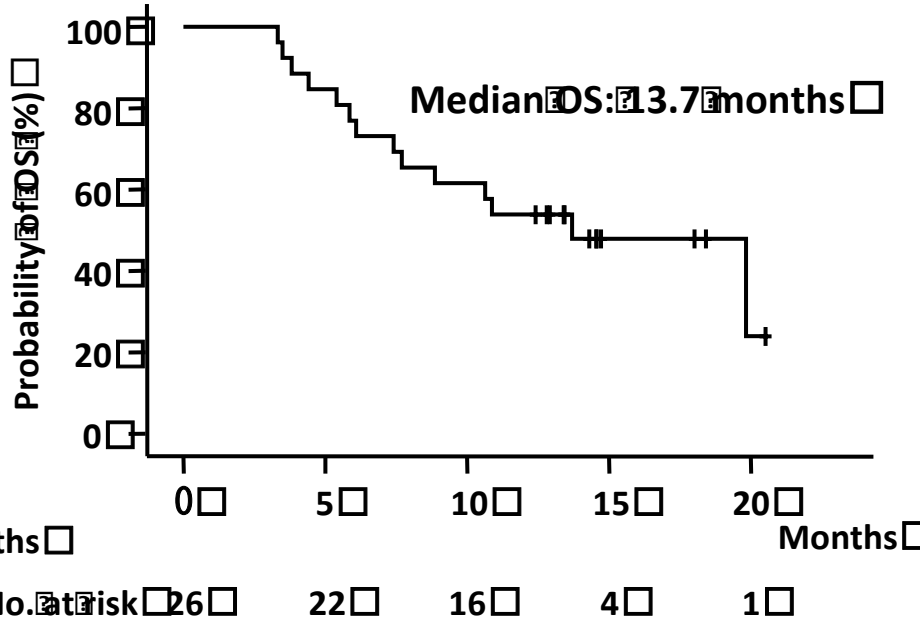
Clinical efficacy of KW-0761

	Best response					Response rate
	CR	PR	SD	PD	Not assessable	≥PR
	number of patients					*no. (%) [95% CI]*
Overall	26	8	5	2	11	0	13 (50%) [30-70]

For relapsed ATL patients



For relapsed ATL patients



Ishida T, Ogura M, et al. J Clin Oncol 2012;30:837

Drug Related Adverse Events (AEs) (n=27) by CTCAE v3.0 (0761-002 Phase II study)

Non-Hematologic AEs	Pts affected, n: Grade 3	Grade 4	All Grades	
infusion reaction	1	0	24	89%
Rash	5	0	17	63%
ALT increased	2	0	11	
AST increased	2	0	10	
Hypoxemia	3	0	5	
γ-GTP increased	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	

*Stevens-Johnson syndrome

Hematologic AEs	Pts affected, n: Grade 3	Grade 4	All Grades
Lymphopenia**	9	11	26
Leukocytopenia	8	0	18
Thrombocytopenia	3	2	14
Neutropenia	5	0	14
Hemoglobin decreased	1	0	8

Ishida T, Ogura M, et al. J Clin Oncol. 2012;30:837

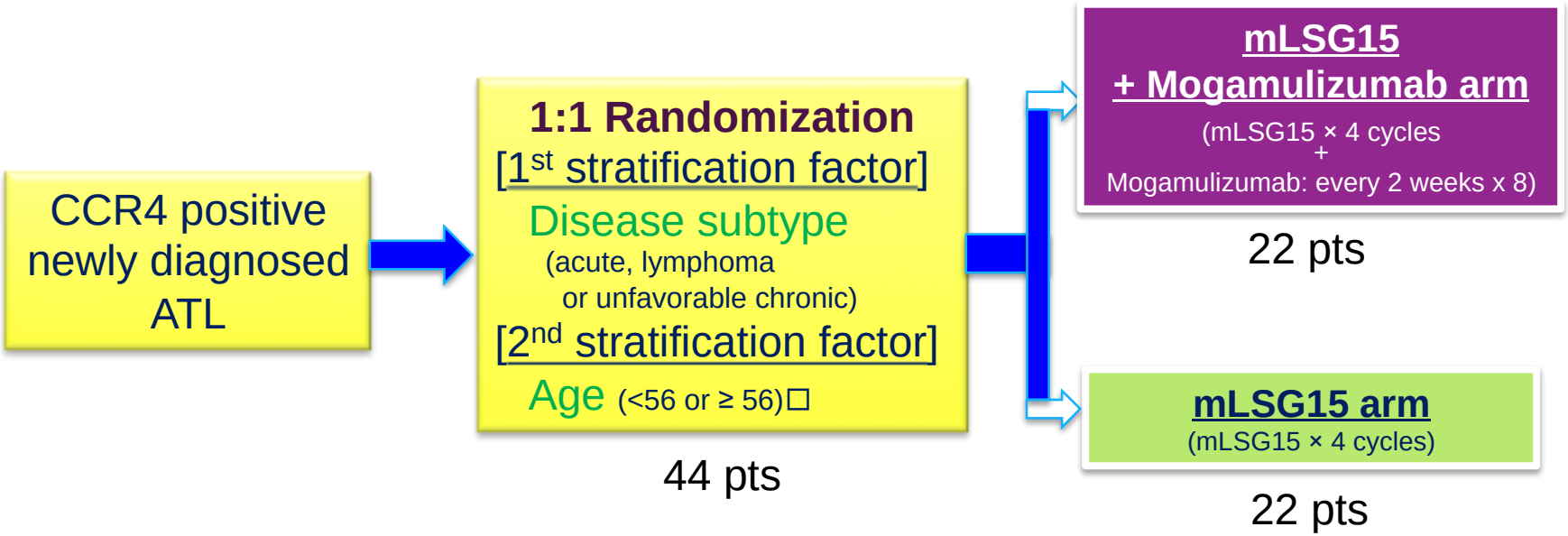
Summary of Phase II Study of KW-0761

- Most common AEs: infusion reaction and rash as well as hematologic ones such as lymphopenia, thrombocytopenia and neutropenia
- Grade 3 rash: Observed in 5 pts. But, they disappeared or improved by steroid treatments
- **ORR: 50% (13/26; 95% CI, 30 – 70%)**
- median PFS, 5.2 months; median OS, 13.7 months

Conclusion:
KW-0761 is an effective agent with acceptable toxicity profiles for pts with relapsed ATL, in which no standard therapy exists. Further investigations are warranted.

Ishida T, Ogura M, et al. J Clin Oncol 2012;30:837

Randomized Phase II study design in newly diagnosed ATL



Endpoints

1. **CR rate**
2. ORR, and ORR according to disease lesion, PFS, OS, Safety, PK

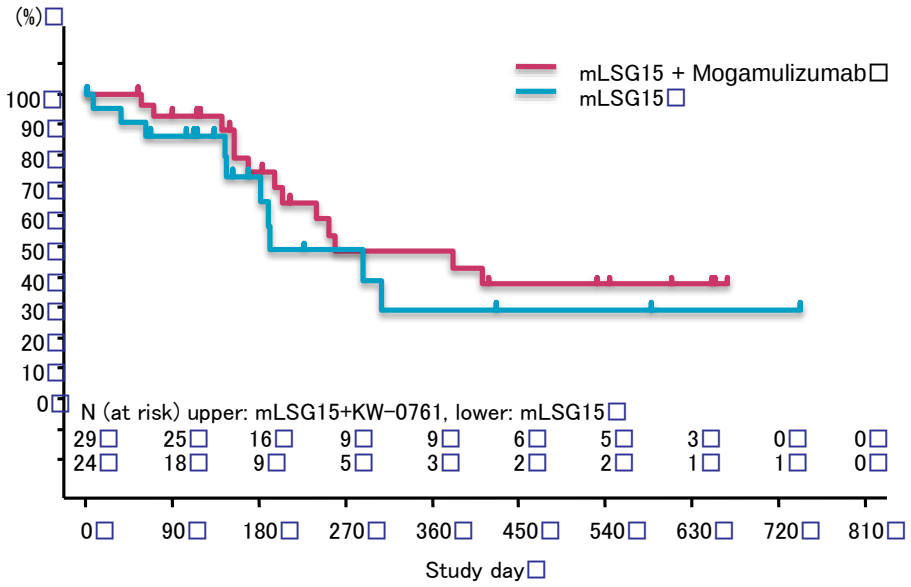
Ishida T. et al. Br J Haematol. 2015 169:672-82.

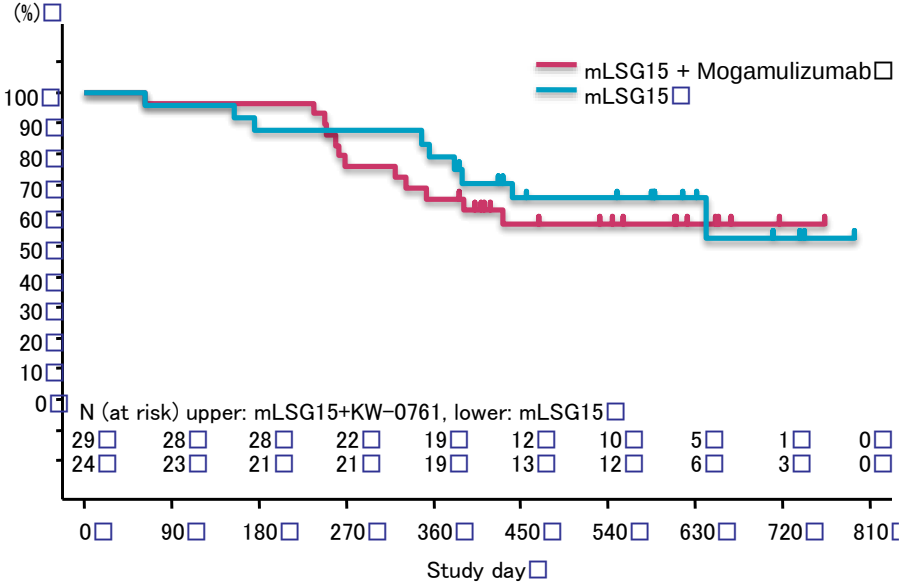
CR rate and ORR□

	mLSG15 + Mogamulizumab (n=29)	mLSG15 (n=24)□
CR□	9□	5□
CRu□	6□	3□
PR□	10□	10□
Number of complete responders□	15□	8□
CR rate (95%CI)□	52% (33~71)□	33% (16~55)□
Number of responders□	25□	18□
ORR (95%CI)□	86% (68~96)□	75% (53~90)□

Ishida T, et al. Br J Haematol. 2015 169:672-82.

PFS and OS□





Group□	N□	Kaplan-Meier estimate□	
		Median PFS (days)□	(95%CI)□
mLSG15 + Mogamulizumab□	29□	259□	(197, -)□
mLSG15□	24□	192□	(147, -)□

Group□	N□	Kaplan-Meier estimate□	
		Median OS (days)□	(95%CI)□
mLSG15 + Mogamulizumab□	29□	-□	(332, -)□
mLSG15□	24□	-□	(389, -)□

Ishida T, et al. Br J Haematol. 2015 169:672-82.

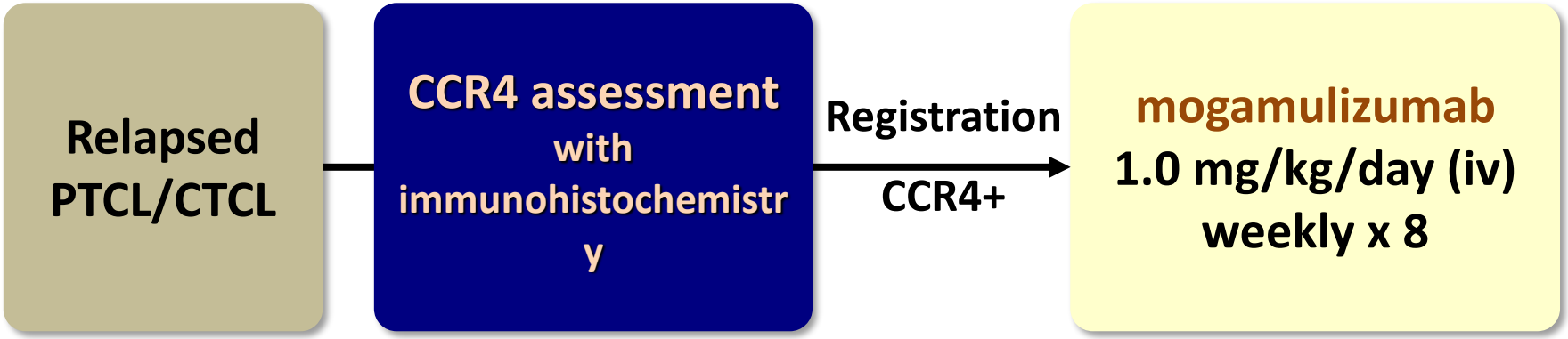
Conclusions

Mogamulizumab with mLSG15

- Higher in CR rate than mLSG15 (52% vs 33%).
- Well tolerated.
- Skin disorders were more frequent, but manageable.
- A reasonable treatment option for newly diagnosed aggressive ATL.
  - *Further investigation is needed because of the small sample size and short follow-up period of this study.*

Phase II study (0761-004) design in relapsed PTCL

Multicenter open labeled study in Japan



- 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)

Ogura M, et al. J Clin Oncol. 2014 32:1157-63.

Efficacy assessment* (n=37)

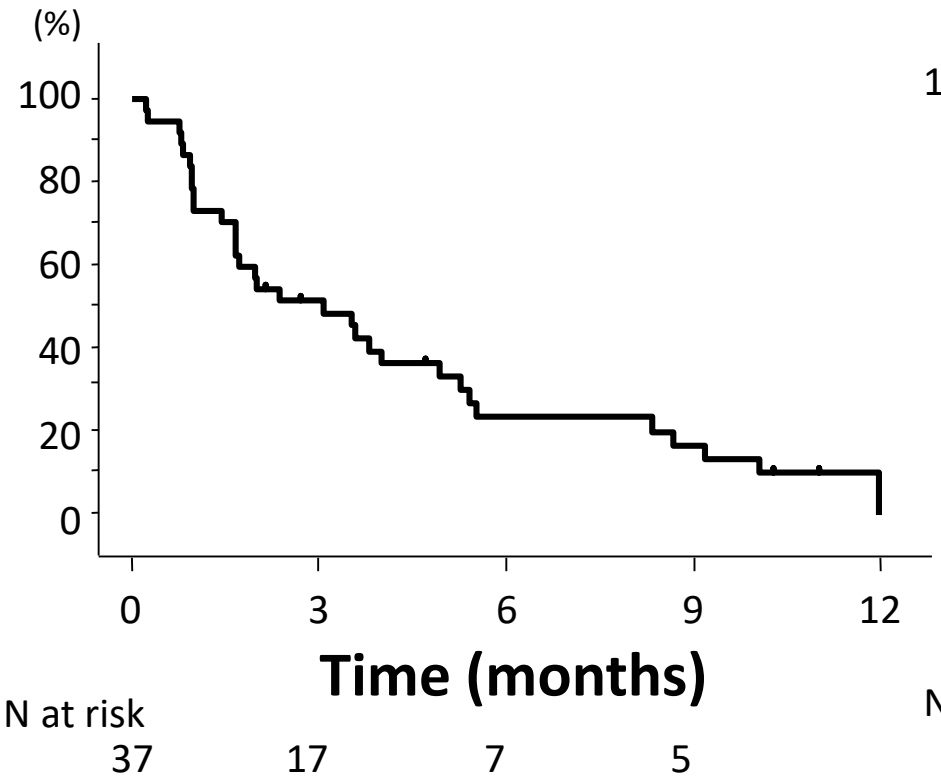
Lymphoma Subtype	N	Best Response				ORR (%) [95% CI]	
		CR	PR	SD	PD		
PTCL	29	5	5	9	10	34	[18-54]
PTCL-NOS	16	1	2	6	7	19	
AITL	12	3	3	3	3	50	
ALCL ALK(-)	1	1 (CRu)	0	0	0	100	
CTCL	8	0	3	4	1	38	[9-76]
MF	7	0	2	4	1	29	
C-ALCL	1	0	1	0	0	100	
Total	37	5	8	13	11	35	[20-53]

*Evaluated by Efficacy Assessment Committee

Ogura M, et al. J Clin Oncol. 2014 32:1157-63.

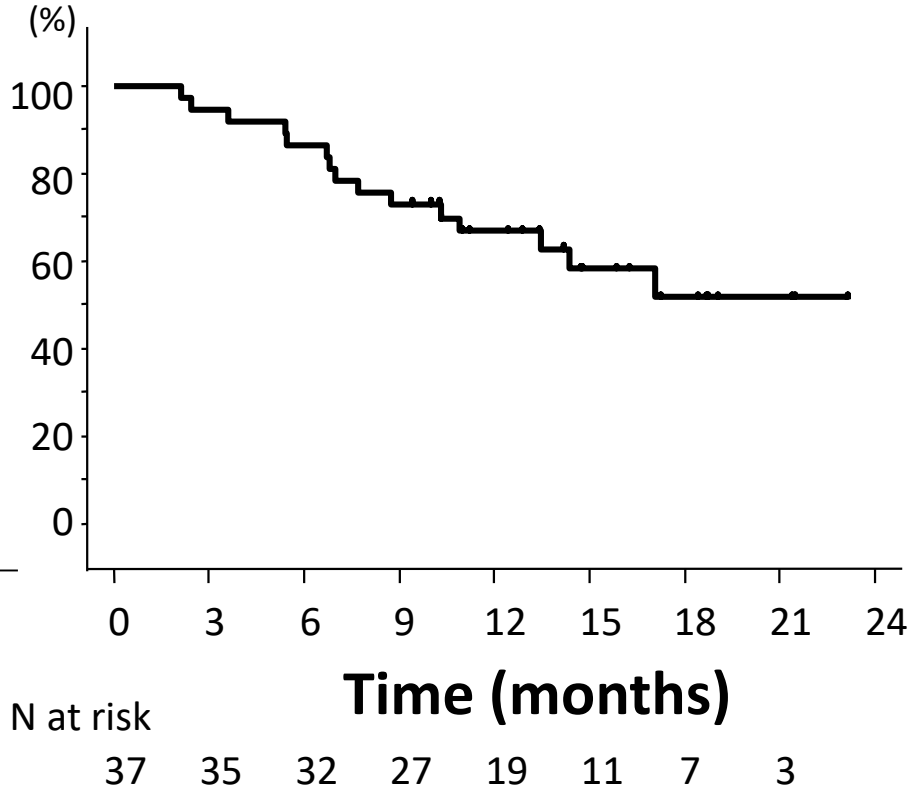
Progression-free survival (PFS)

	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. J Clin Oncol. 2014 32:1157-63.

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%

In 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

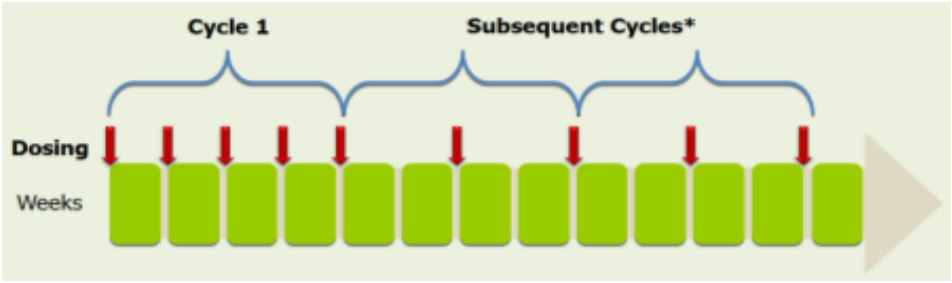
Conclusions

- **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.

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]

Comparison of Phase II studies in Japan and EU

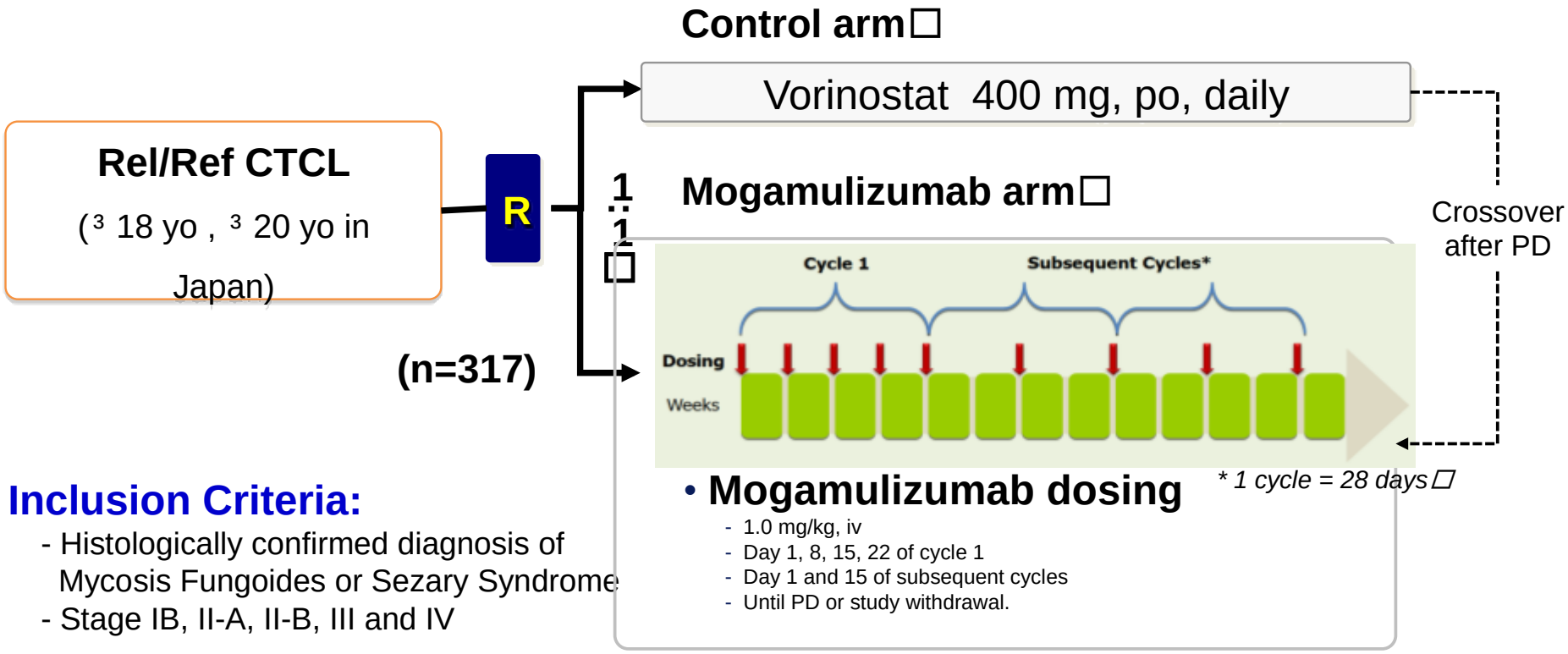
	P-2 in Japan	P-2 in EU
PS 2	0.4%(1/37) *	39%(15/38)
Median No. of previous systemic therapy	2 (1-6)	2 (1-8)
Refractory to last systemic therapy	0% (not eligible)	45% (17/38)
Schedule of Moga* administration	1 mg/week x 8 weeks	1mg/week x 4 weeks 1 mg/ 2 weeks from 5th dose until PD
Median No. of administered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

KW-0761-010 : Phase III Trial for Cutaneous T Cell Lymphoma (the Phase III MAVORIC Study)



- **Inclusion Criteria:**
  - Histologically confirmed diagnosis of Mycosis Fungoides or Sezary Syndrome
  - Stage IB, II-A, II-B, III and IV

- **Primary objective:** PFS

- **Status:** Patient enrollment completed

- **Countries:**

  United States, Australia, Denmark, France, Germany, Italy, Japan, Netherlands, Spain, Switzerland, United Kingdom

Kim YH, et al., Lancet Oncol. 2018, 19:1192-1204.

ClinicalTrials.gov ID: NCT01728805

MAVORIC: PFS (Primary Endpoint)

- **Significantly longer PFS with mogamulizumab** vs vorinostat
  - Median PFS: 7.7 mos vs 3.1 mos; HR: 0.53 (95% CI: 0.41-0.69; *P* < .0001)
- PFS improved in most predefined pt subgroups

Group	PFS HR (95% CI)	*P* Value
ITT (n = 372)	0.53 (0.41-0.69)	< .0001
Female (n = 156)	0.62 (0.41-0.94)	.0275
Male (n = 216)	0.46 (0.33-0.65)	< .0001
< 65 yr of age (n = 188)	0.59 (0.41-0.85)	.0009
≥ 65 yrs of age (n = 184)	0.46 (0.31-0.68)	.0004
Mycosis fungoides (n = 204)	0.72 (0.51-1.01)	.0675
Sézary syndrome (n = 168)	0.32 (0.21-0.49)	< .0001
Stage IB/II (n = 140)	0.88 (0.58-1.35)	.7166
Stage III/IV (n = 232)	0.36 (0.26-0.51)	< .0001

Group	PFS HR (95% CI)	*P* Value
White (n = 260)	0.51 (0.37-0.70)	< .0001
Black (n = 37)	0.79 (0.32-1.92)	.6391
Other (n = 75)	0.50 (0.28-0.91)	.0323
US (n = 201)	0.49 (0.34-0.70)	< .0001
Europe/Australia (n = 156)	0.61 (0.41-0.91)	.0171
Japan (n = 15)	0.28 (0.05-1.58)	.1583
Normal or low LDH (n = 194)	0.62 (0.43-0.88)	.0075
Elevated LDH (n = 173)	0.41 (0.27-0.61)	< .0001

Kim YH, et al., Lancet Oncol. 2018, 19:1192-1204.

MAVORIC:Conclusions

- Mogamulizumab significantly improved PFS, ORR vs vorinostat in pts with previously treated CTCL
  - Median PFS: 7.7 vs 3.1 mos; HR: 0.53 (95% CI: 0.41-0.69; *P* < .0001)
  - ORR: 28.0% vs 4.8% (*P* < .0001)
- Pt-reported QoL outcomes improved with mogamulizumab
- Safety profile in this trial was similar to previous reports and common AEs were manageable
- Mogamulizumab could provide a new, effective treatment for patients with mycosis fungoides and, importantly, for Sézary syndrome

Kim YH, et al., Lancet Oncol. 2018, 19:1192-1204.

Possible Future Directions

- **Combination of mogamulizumab with lenalidomide in PTCL**
  - **Ogura M, et al. Lenalidomide in relapsed ATL or PTCL. Lancet Haematol 2016; 3: e107-18**
- **Combination of mogamulizumab with PD-1 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**
- **Sequential use of mogamulizumab followed by HDAC inhibitors in PTCL**
- **etc**

Thank you for your attention