New Drugs in Hematology

Development of Mogamulizumab, a defucosylated anti-CCR4 humanized monoclonal antibody

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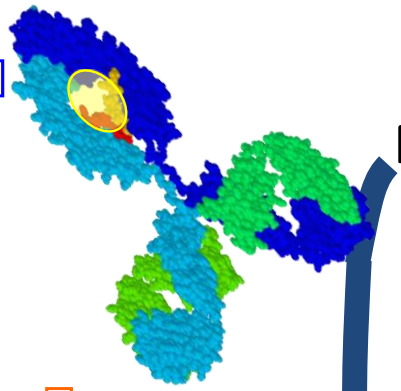
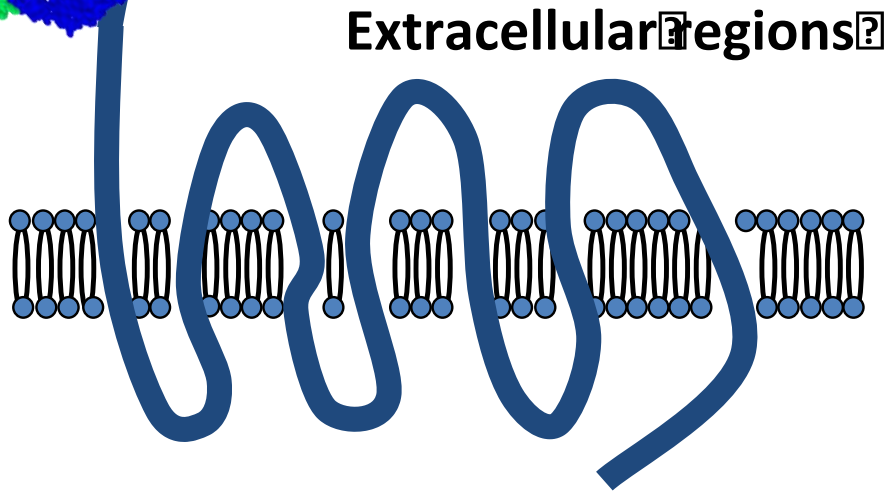
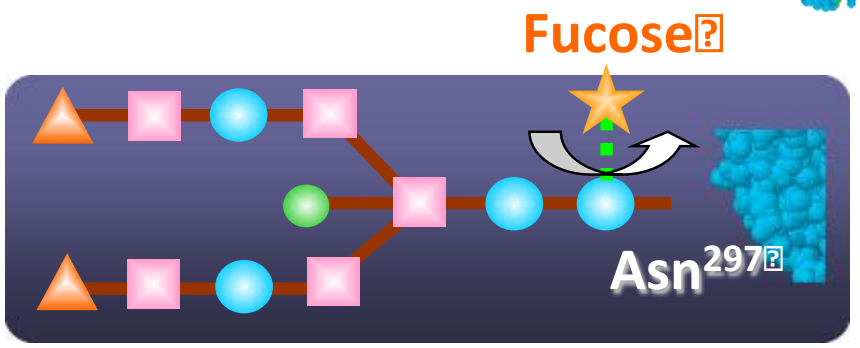
Mogamulizumab (KW-0761) : Drug Profile







Higher ADCC due to a defucosylated Fc region by POTELLIGENT®

Shinkawa et al, J Biol Chem 2003;278:3466
Niwa et al, Cancer Res 2004;64:2127
Ishii et al, Clin Cancer Res 2010;16:1520

CCR4 (CC chemokine receptor 4)

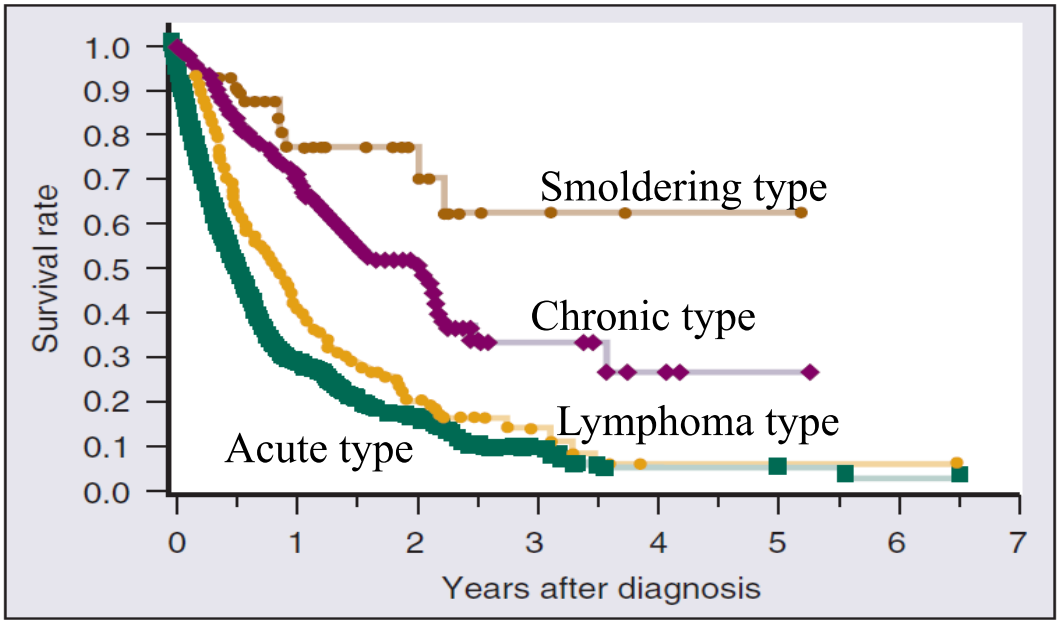
GPCR for MDC and TARC
Markers for Type II helper T-cells and Regulatory T-cells (FoxP3+)
Over-expressed in ATL, PTCL and CTCL

Ishida et al, Clin Cancer Res 2003;9:3625
Ishida et al, Clin Cancer Res 2004;10:5494

GPCR: G protein-coupled receptor
MDC: macrophage-derived chemokine
TARC: thymus and activation-regulated chemokine

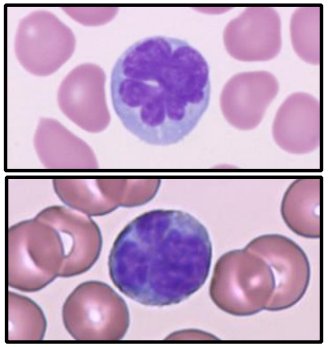
Adult T-cell leukemia lymphoma (ATL)

ATL patients (pts) have very poor prognosis

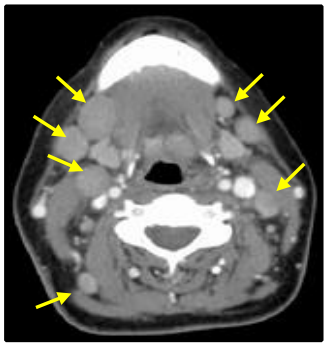


Disease Subtype	MST (mon)	Survival Rate(%)	
		2-year	4-year
Smoldering	-	77.7	62.8
Chronic	24.3	52.4	26.9
Lymphoma	10.2	21.3	5.7
Acute	6.2	16.7	5.0

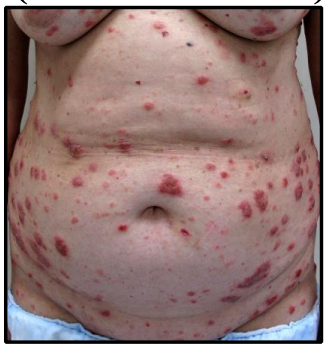
ATL cells frequently infiltrate into systemic organs.



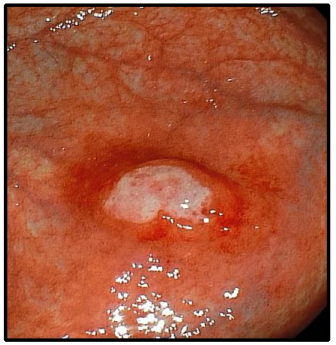
blood ATL cells (flower like cells)



LN lesion



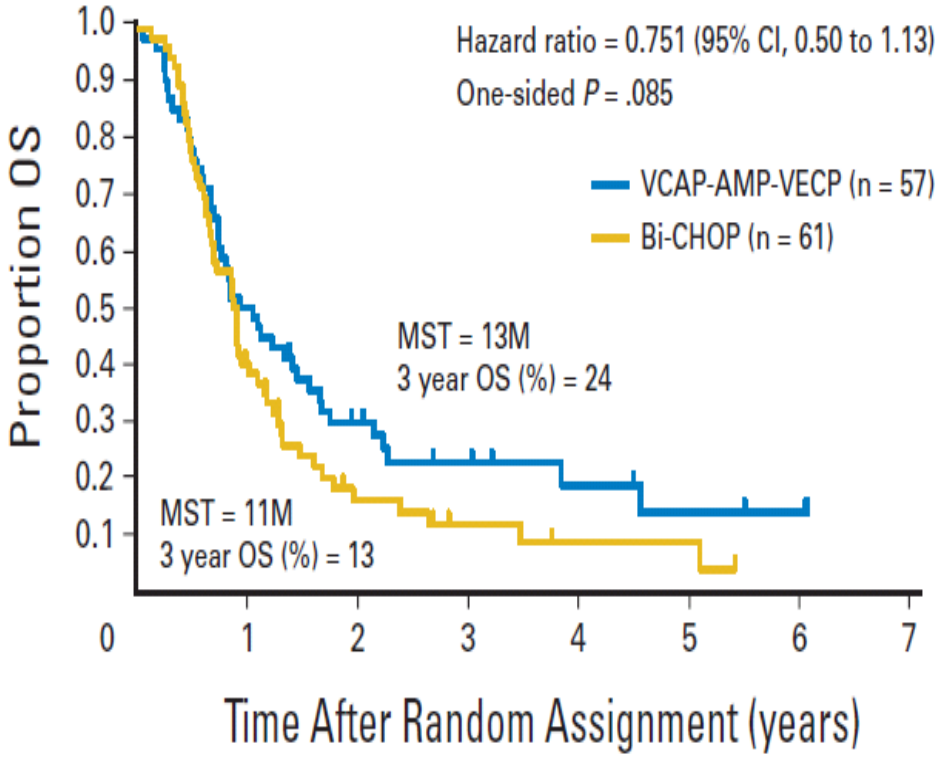
skin lesion



gastric lesion

Shimoyama, Br J Haematol 1991;79:428

Treatments for aggressive ATL in Japan (~2010)



Tsukasaki et al, J Clin Oncol 2007;25:5458

Other agents for relapsed ATL

Agents	Response rates
MST-16	0% (0/4)
CPT-11	38% (5/13)
2'-Deoxycoformycin*	32% (10/31)
Cladribine	7% (1/15)

Ohno, Ogura, et al., Cancer 1993;71:2217
Tsuda et al, Br J Cancer 1994;70:771
Tobinai et al, Jpn J Clin 1992;22:164
Tobinai, Ogura et al, Int J Hematol 2003;77:512

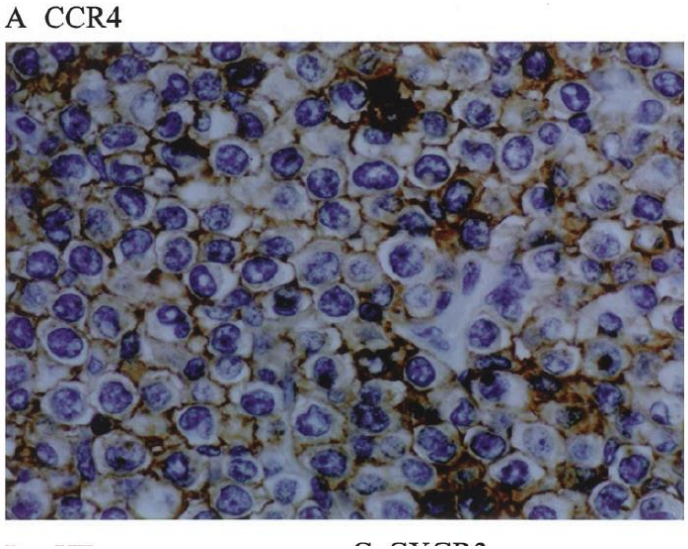
First line Chemotherapy : mLSG15 (VCAP-AMP-VECP), CHOP etc.

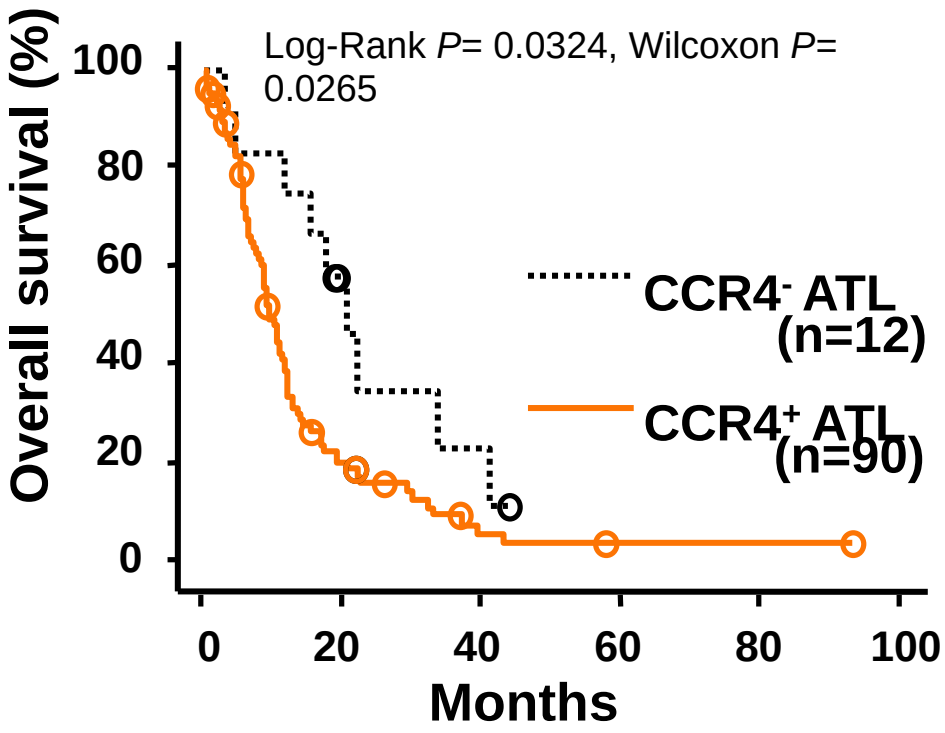
Limited treatment options for relapsed ATL

CCR4 expression in ATL

91 (88.3 %) of the 103 cases of patients with ATL were positive for CCR4. Multivariate analysis confirmed that CCR4 expression was an independent and significant prognosis factor .

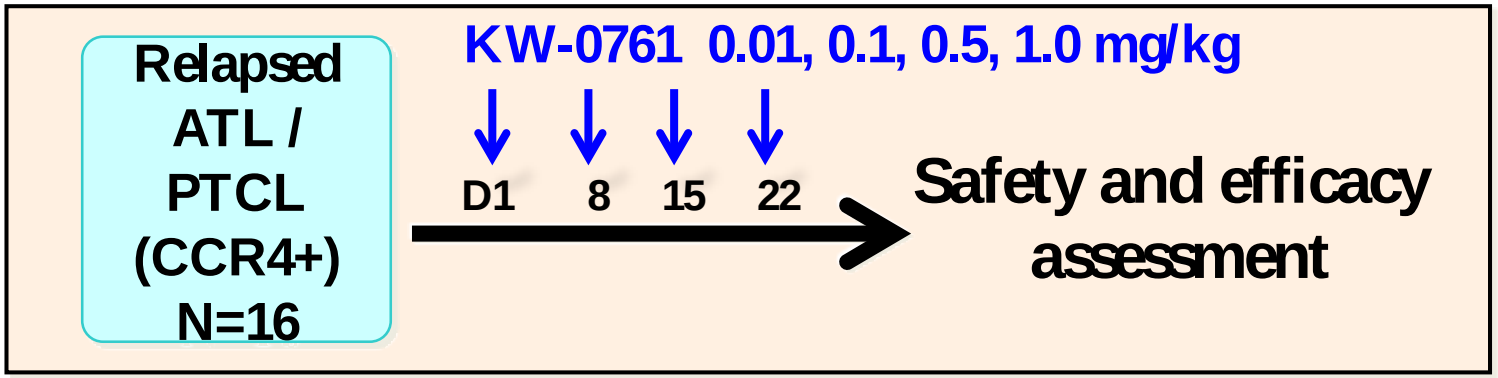
Ishida et al, Clin Cancer Res 2003; 9: 3625





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

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

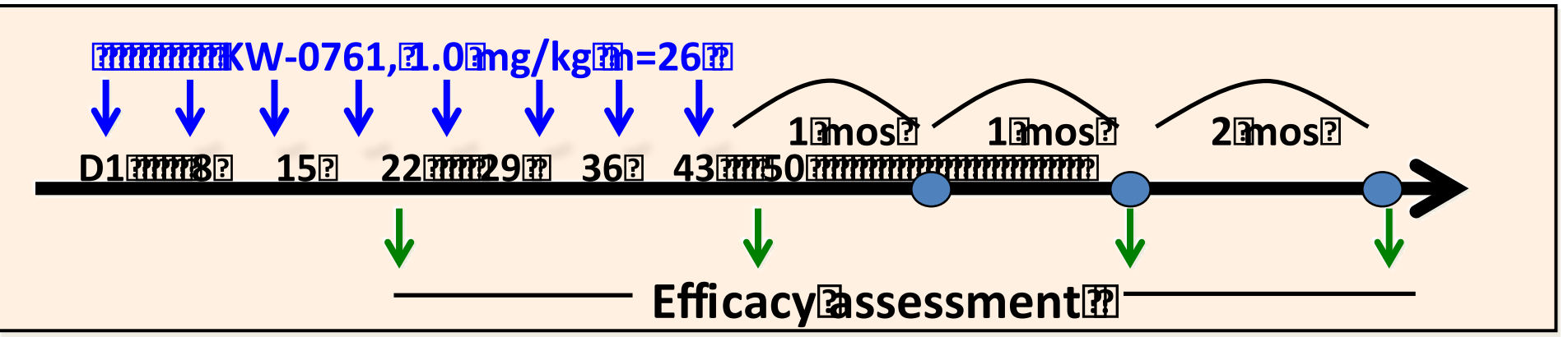


- **One out of six patients @1 mg/kg cohort exhibited DLTs including G4 neutropenia, G3 febrile neutropenia and G3 rash.**
- **44% (7/16) of ≥ G2 acute infusion reaction/cytokine release syndrome was observed and their reactions were tolerable.**
- **$T_{1/2}$ at 1.0 mg/kg after the 4th dosing was 454 h± 164 h (18.9 ± 6.8 day).**
- **No anti-KW-0761 antibody**
- **Investigator-assessed responses for 16 enrolled patients: RR 31% (5/16 patients) including 3 CRs and 2 PRs.**
- **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 of KW-0761 in CCR4 + Relapsed ATL

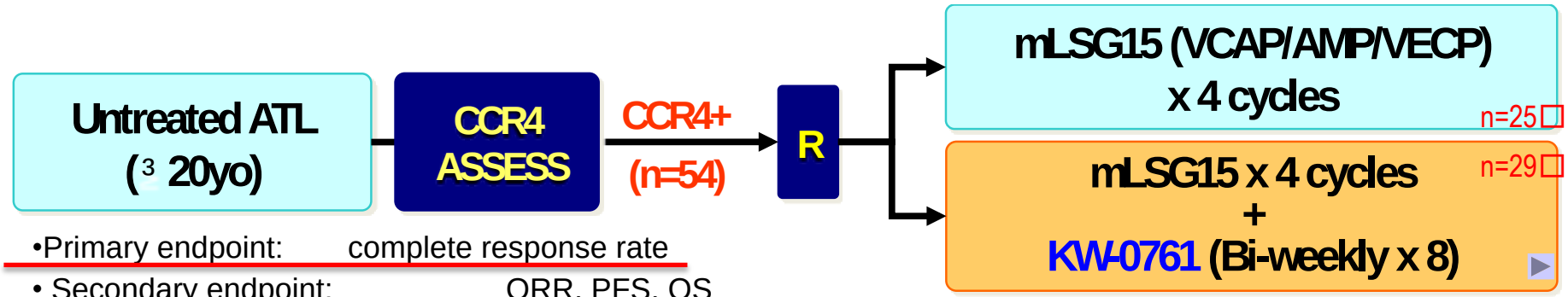
A multicenter open labeled pivotal study in Japan



- **50% of ORR (13/26; 95% CI, 30 - 70) met the primary endpoint defined as the best overall response (Threshold; 5%, Expected; 30%). ORR for disease sites are: Blood (100%; 13/13), Skin (63%; 5/8), Lymph node (25%; 3/12).**
- **Major 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.**
- ***Launched for treatment of CCR4+ r/r ATL May 2012 in Japan***

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

A pivotal phase II study of mogamulizumab for newly diagnosed ATL



•Primary endpoint: complete response rate

• Secondary endpoint: ORR, PFS, OS

ClinicalTrials.gov ID:NCT01173887

	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)

Indication expansion to untreated CCR4+ ATL with chemo Dec 2014 in Japan

Ishida T et al. BJH 2015, 196 : 672

ATL-Treatment in the US and EU

Region (first-line treatment)	Comment
NCCN (North America) 1)Chronic/smoldering subtypes: a)Zidovudine/interferon, or b)Skin directed therapy if clinically indicated, or c)Observation, or d)Clinical trial.	-For those responded to Zidovudine/interferon, continue treatment.
2)Acute subtype a)Zidovudine/interferon, or b)Chemotherapy*, or c)Clinical trial.	-For those responded to treatment, continue prior treatment or consider allogeneic stem cell transplantation.
3)Lymphoma subtype a)Chemotherapy*, or b)Clinical trial.	-For those responded to treatment, continue chemotherapy or consider allogeneic stem cell transplantation.
*CHOP, CHOEP, dose adjusted EPOCH, or hyper CVAD alternating with high dose methotrexate and cytarabine	

- **No approved anti-ATL agents in Europe or USA**
- **For Acute type, AZT and IFN-α also used**
- **For aggressive forms, several salvage therapies are used:**
  - **CHOP, EPOCH, GemOx, DHAP, hyper CVAD, Pralatrexate**

KW-0761-009 Phase II Trial for relapsed/refractory ATL

Relapsed/ Refractory ATL
(≥18 yo)
(n=70)

R

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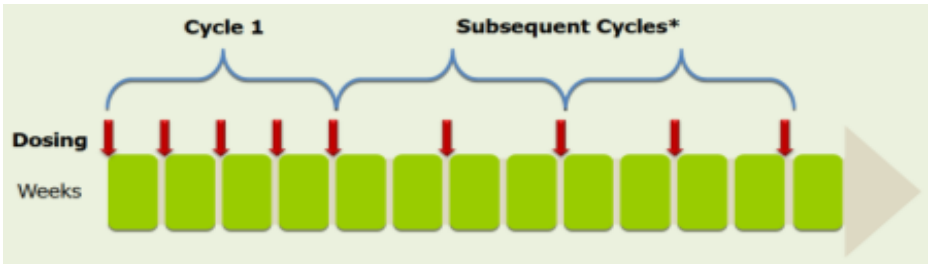
Control arm (n=23)

Investigator's choice:

Pralatrexate, DHAP, or GemOx

Mogamulizumab arm (n=47)



** 1 cycle = 28 days*

- **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.

Crossover after PD

- **Inclusion Criteria:**
  Confirmed diagnosis of ATL (excluding smoldering subtype)

- **Primary objective**: ORR

- **Status**:
  Patient enrollment completed

- **Countries**:
  US, UK, France, Romania, Brazil, Peru, Martinique

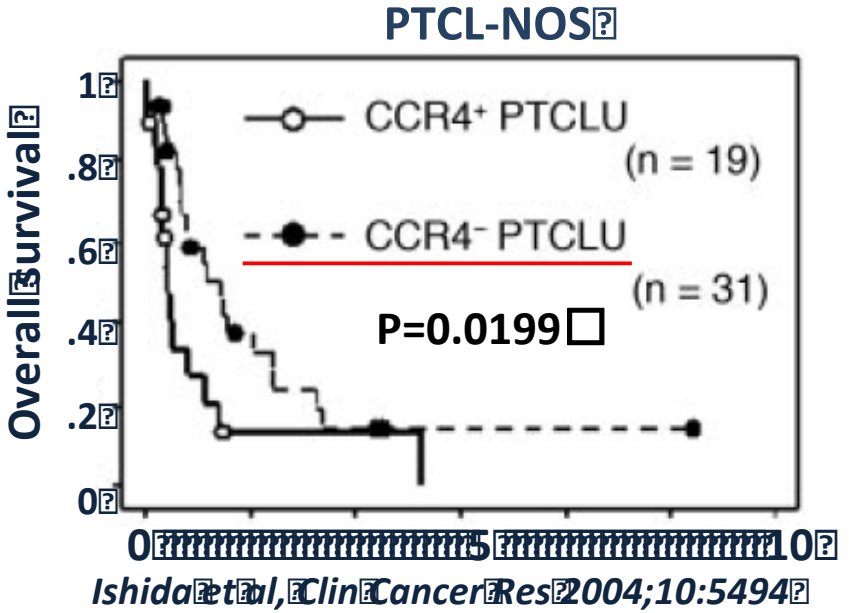
ClinicalTrials.gov ID: NCT01626664

CCR4 expression and prognosis of PTCL/CTCL

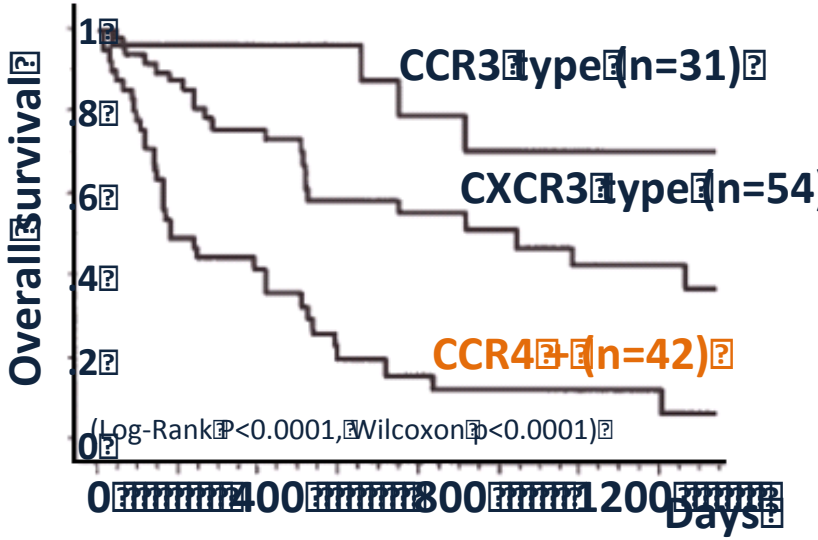
Mature T-cell and NK-cell neoplasms

- 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%)

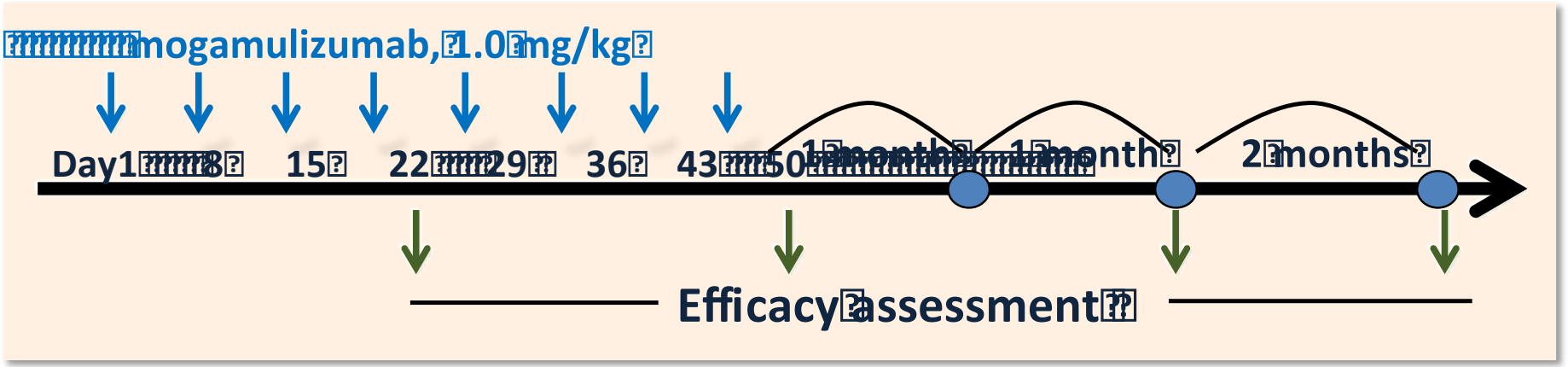
Ishida et al, Clin Cancer Res 2003;9:362
Ishida et al, Clin Cancer Res 2004;10:5494
Ishida et al, Int J Hematol 2005;82:148
Ishida et al, Leukemia 2006;20:2162
Yano et al, Clin Cancer Res 2007;13:6494



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



Phase II study for relapsed CCR4+ PTCL and CTCL in Japan

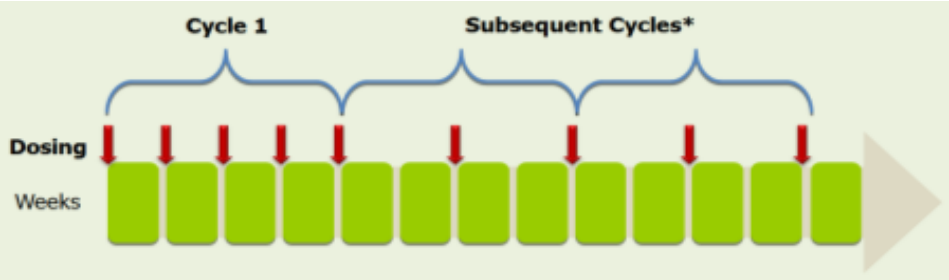


Lymphoma Subtype	N	Best Response				ORR(%)	[95% CI]
		CR	PR	SD	PD		
PTCL	29	5	5	9	10	34	[18-54]
PTCL-NOS	16	1	2	6	7	19	
AITL	12	3	3	3	3	50	
ALCL ALK(-)	1	1(CRu)	0	0	0	100	
CTCL	8	0	3	4	1	38	[9-76]
MF	7	0	2	4	1	29	
C-ALCL†	1	0	1	0	0	100	
Total	37	5	8	13	11	35	[20-53]

Indication expansion to r/r CCR4+ PTCL and CTCL April 2014 in Japan

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

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



- **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.

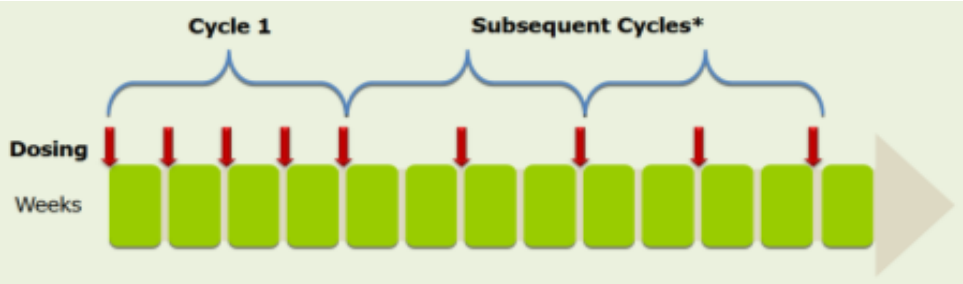
Overall Response by Histological Subtype

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%)

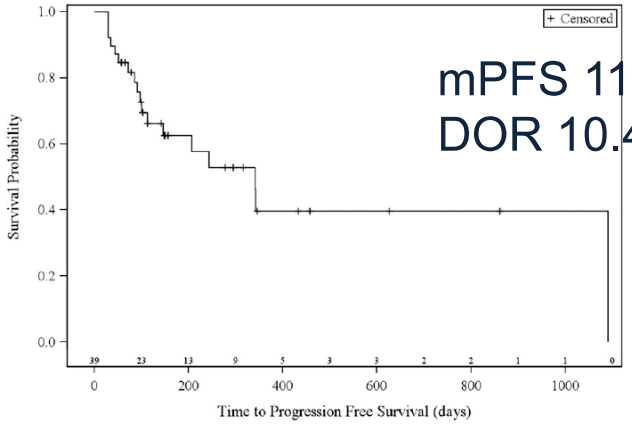
a: One patient had CR by CT scan but did not have bone marrow done for confirmation of CR.

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

Phase I/II study for r/r CTCL in the US



- **Mogamulizumab dosing**
  - Phase I: 0.1, 0.3, 1.0 mg/kg, Phase II 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.



mPFS 11.4 months
DOR 10.4 months

All evaluable CTCL pts (n = 38)	Blood (n = 19)	Skin (n = 38)	LNs (n = 28)	Global response (n = 38)
ORR, n (%) [95% CI]	**18 (95%)**	**16 (42%)**	**7 (25%)**	**14 (37%)** [22 - 54%]
CR	11 (58%)	4 (11%)	4 (14%)	3 (8%)
PR	7 (37%)	12 (32%)	3 (11%)	11 (29%)
SD	1 (5%)	20 (53%)	17 (61%)	19 (50%)
PD	0 (0%)	2 (5%)	4 (14%)	5 (13%)

ORR was 37%: 47% in Sézary syndrome (n = 17) and 29% in MF (n = 21).

Duvic M et al., Blood 2015, 125: 1883

KW-0761-010 : Phase III Trial for Cutaneous T Cell Lymphoma

Control arm

Vorinostat 400 mg, po, daily

Rel/Ref CTCL

(³ 18 yo , ³ 20 yo in Japan)

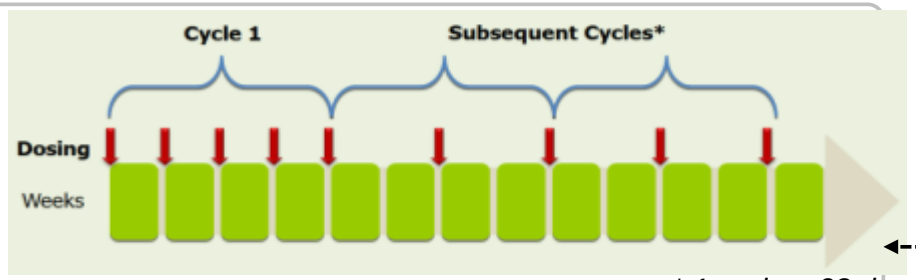
R

1 : 1

Mogamulizumab arm

(n=317)

Crossover after PD



** 1 cycle = 28 days*

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

- **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.

- **Primary objective:** PFS

- **Status:** Patient enrollment completed

- **Countries:**

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

ClinicalTrials.gov ID: NCT01728805

Possible Future Directions

- **Combination of mogamulizumab with lenalidomide in ATL**
  - **Ogura M, et al. Lenalidomide in relapsed ATL or PTCL. Lancet Haematol 2016; 3: e107-18**
  - **Fujiwara H, Ogura M, et al. Multicenter phase II study of lenalidomide in relapsed or recurrent adult T-cell leukemia-lymphoma (ATLL-002). ASH2015**
- **Combination of mogamulizumab with PD-1 blockade in ATL or 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**
- **Combination of mogamulizumab with HDAC inhibitors in PTCL**
- **etc**

Thank you for your attention