2012...2015. T-Cell Lymphomas: We are illuminating the darkest of tunnels
Wednesday, April 29, 2015, Royal Hotel Carlton, Bologna, Italy

Mogamulizumab inside the T-cell family:

# Mogamulizumab for PTCL

Kensei Tobinai, MD, PhD

National Cancer Center Hospital, Tokyo, Japan

# CCR4 Expression and Prognosis in T/NK-Cell Malignancies

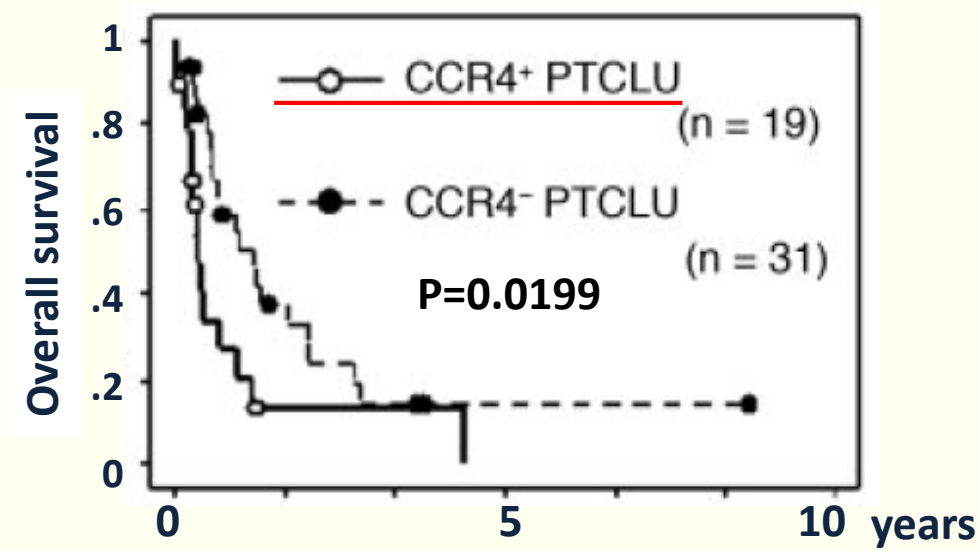
## Peripheral T/NK-cell neoplasms

| | | |
|---|---|---|
| • NK/T, nasal type | 1 /27 | (4%) |
| • **MF in transformation** | **10 /20** | **(50%)** |
| • ALCL, ALK+ | 1 /24 | (4%) |
| • ALCL, ALK- | 8 /16 | (50%) |
| • **PTCL-NOS** | **24 /58** | **(41%)** |
| • **AITL** | **12 /38** | **(32%)** |
| • **ATL** | **108 /120** | **(90%)** |
| • Others | 5 /12 | (42%) |

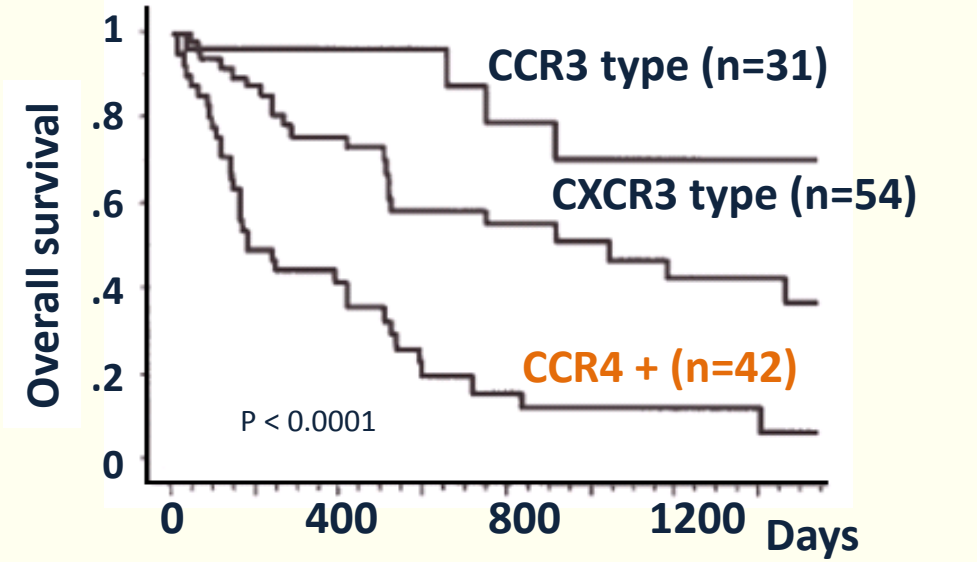
*Ishida T, et al.: Clin Cancer Res 2003;9:362*

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

**PTCL-NOS**




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



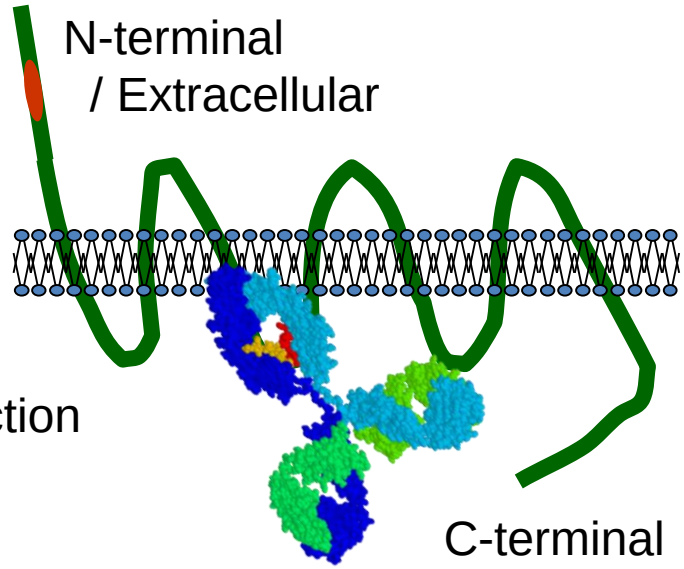

*Ohshima K, et al.: Int J Oncol 2004;25:605 modified*

# CC Chemokine Receptor 4 (CCR4) & Mogamulizumab

## Mogamulizumab

**1. High ADCC**

2. No CDC
3. No direct apoptosis induction
4. No neutralizing activity

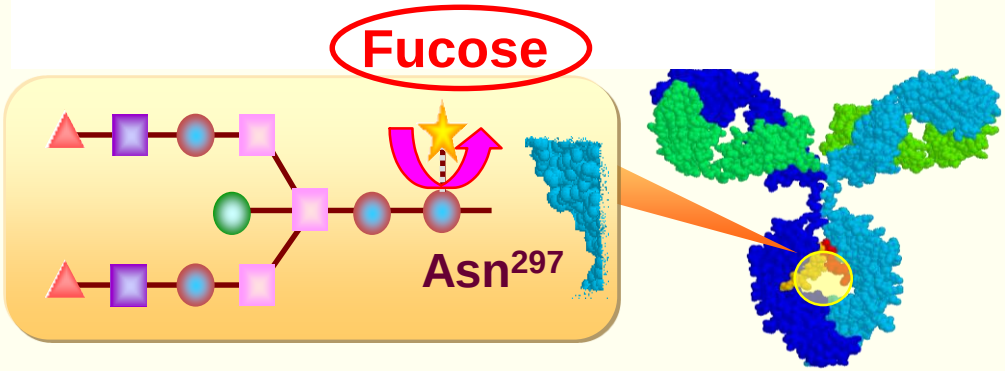



## CCR4

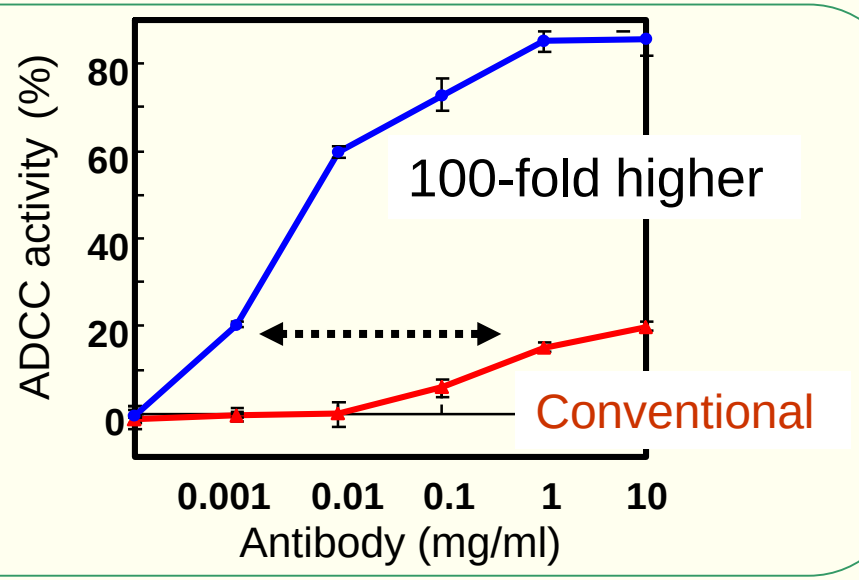
1. 7 Transmembrane G protein coupled receptor (GPCR)
2. TARC & MDC as ligands
3. Expressed on Th2 cells and FOXP3+ Treg cells

## POTELLIGENT® TECHNOLOGY

Defucosylation from the oligosaccharides on the Fc domain




*Niwa R, et al.: Cancer Res 2004;64:2127*



# Japanese Phase II Study of Mogamulizumab in Patients with Relapsed PTCL and CTCL

Ogura M, Ishida T, Tobinai K, Tsukasaki K, Akinaga S, Ueda R, et al.: KW-0761 Study Group in Japan

*J Clin Oncol 2014;32:1157-63*

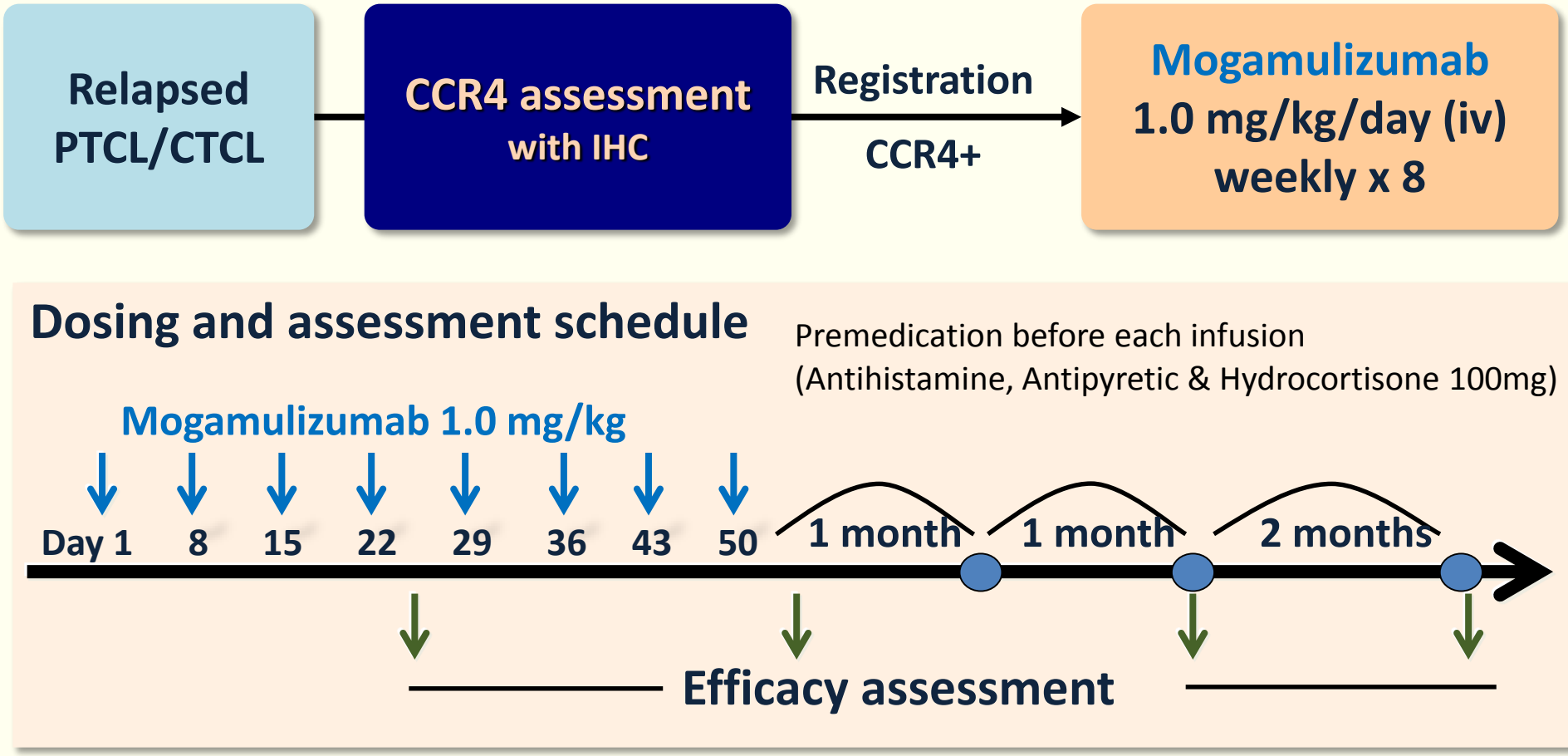
# Phase II Study of Mogamulizumab for PTCL/CTCL: Key Eligibility Criteria

- ***CCR4-positive PTCL or CTCL**
- **Relapsed after the last chemotherapy by which objective response was obtained**
- ECOG PS: 0 – 2
- Age ≥ 20 years
- Normal function of the major organs
- No prior allogeneic SCT
- Negative for HBV surface antigen and HCV antibody

*Subtypes were confirmed by the Central Pathology Review

*Ogura M, Tobinai K, et al.: J Clin Oncol 2014;32:1157-63*

# Phase II Study of Mogamulizumab for PTCL/CTCL: Design




*Ogura M, Tobinai K, et al.: J Clin Oncol 2014;32:1157-63*

# Phase II Study of Mogamulizumab for PTCL/CTCL:
# **Patient Demographics (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** |
| **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 |

*Ogura M, Tobinai K, et al.: J Clin Oncol 2014;32:1157-63*

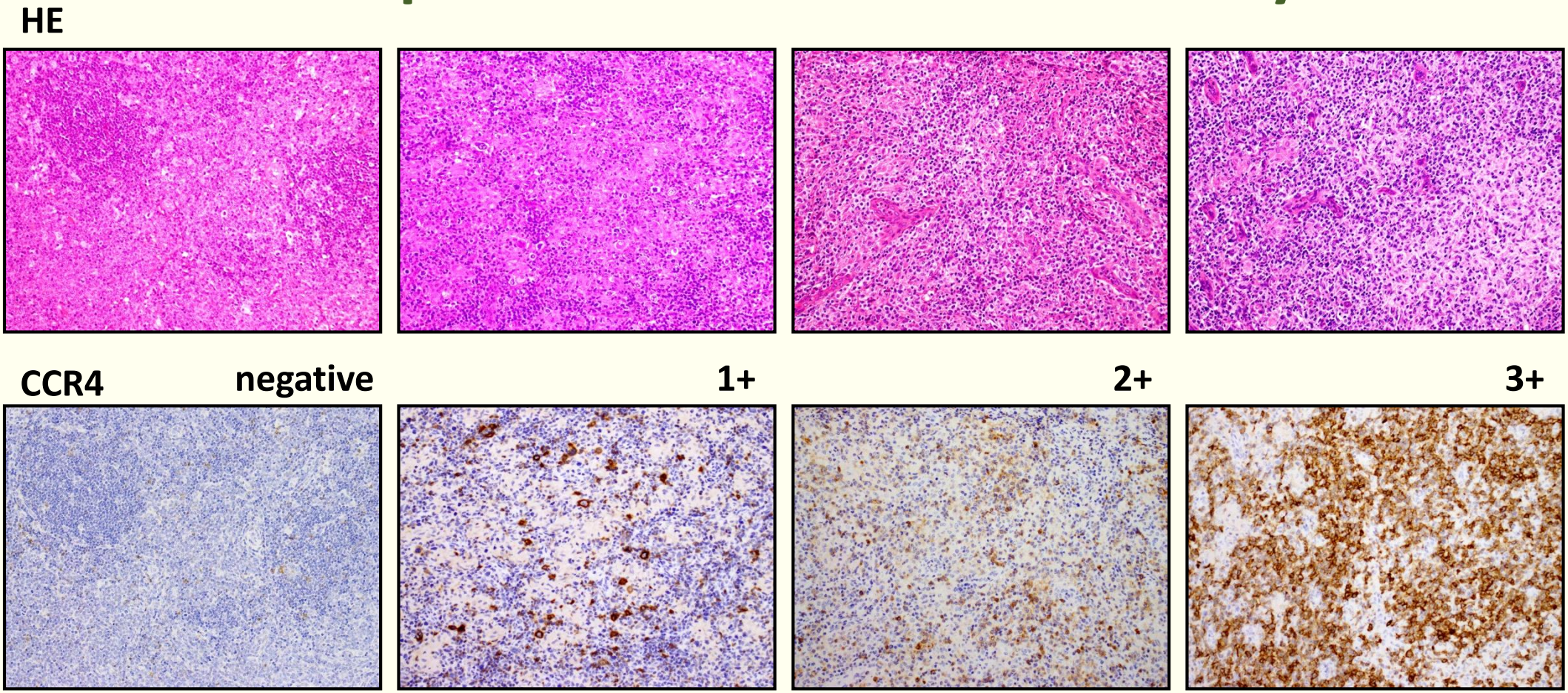
# Phase II Study of Mogamulizumab for PTCL/CTCL: **Efficacy Assessment* (n=37)**

| 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 / †Cutaneous ALCL

*Ogura M, Tobinai K, et al.: J Clin Oncol 2014;32:1157-63*

# CCR4 Expression Levels Determined by IHC



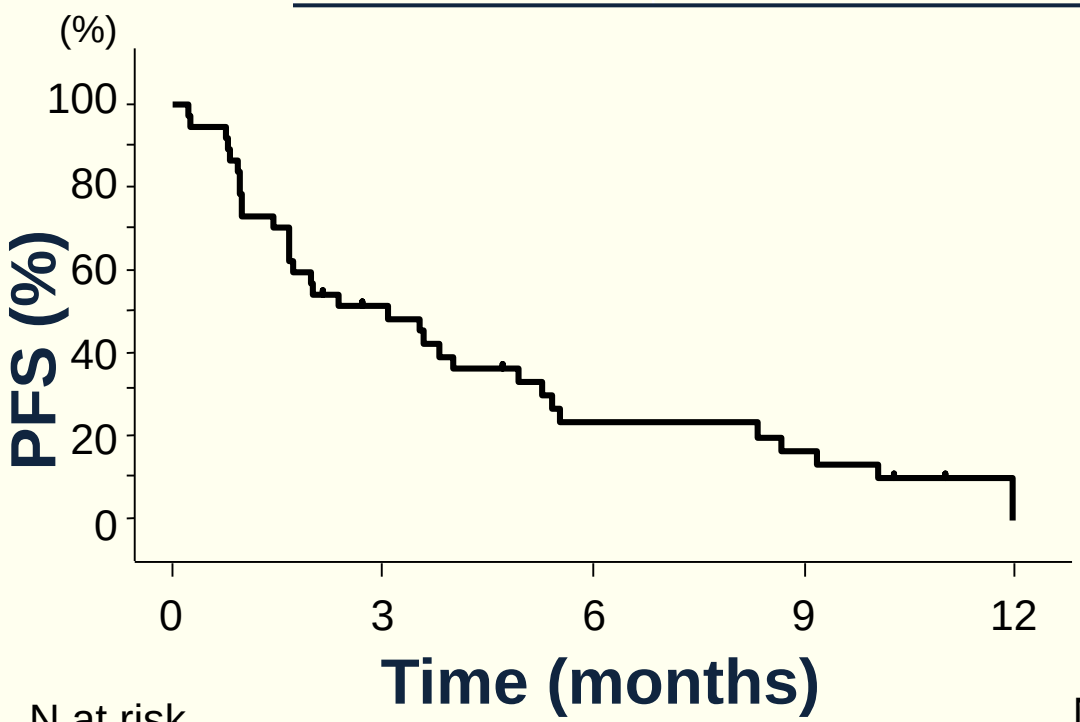

There was no correlation between ORR and CCR4 expression level.

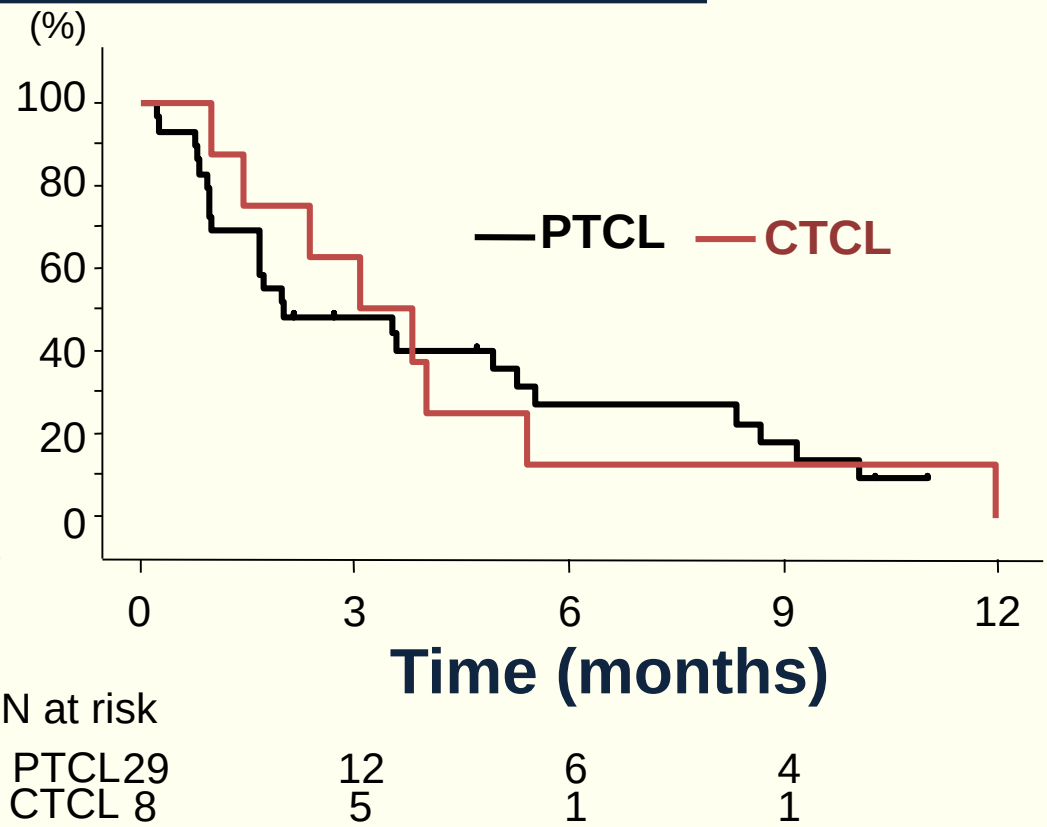
| | | Tumor cells |
|---|---|---|
| CCR4 negative | | < 10% |
| CCR4 positive | 1+ | 10≤ <25% |
| | 2+ | 25≤ <50% |
| | 3+ | 50% |

*Ogura M, Tobinai K, et al.: J Clin Oncol 2014;32:1157-63*

# Phase II Study of Mogamulizumab for PTCL/CTCL: **Progression-free Survival (PFS)**

| | Median PFS (months) | [95% CI] |
|---|---|---|
| Total | 3.0 | [1.6 - 4.9] |
| PTCL | 2.0 | [1.0 - 5.2] |
| CTCL | 3.4 | [1.0 - 5.3] |




*Ogura M, Tobinai K, et al.: J Clin Oncol 2014;32:1157-63*

# Mogamulizumab for PTCL/CTCL: **Adverse Events* (n=37)**

| Non-Hematologic AEs | Patients affected, N: Grade 3 | Grade 4 | All Grades | |
|---|---|---|---|---|
| Pyrexia | 0 | 0 | 11 | 30% |
| Rash | 2 | 0 | 10 | 27% |
| 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 esophagitis | 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 3 | Grade 4 | All Grades | |
|---|---|---|---|---|
| Lymphopenia | 16 | 11 | 30 | 81% |
| Leukocytopenia | 3 | 2 | 16 | 43% |
| Neutropenia | 4 | 3 | 14 | 38% |
| Thrombocytopenia | 0 | 1 | 14 | 38% |
| Anemia | 1 | 1 | 5 | 14% |
| Febrile Neutropenia | 1 | 0 | 1 | 3% |

*Possibly/probably/definitely drug-related

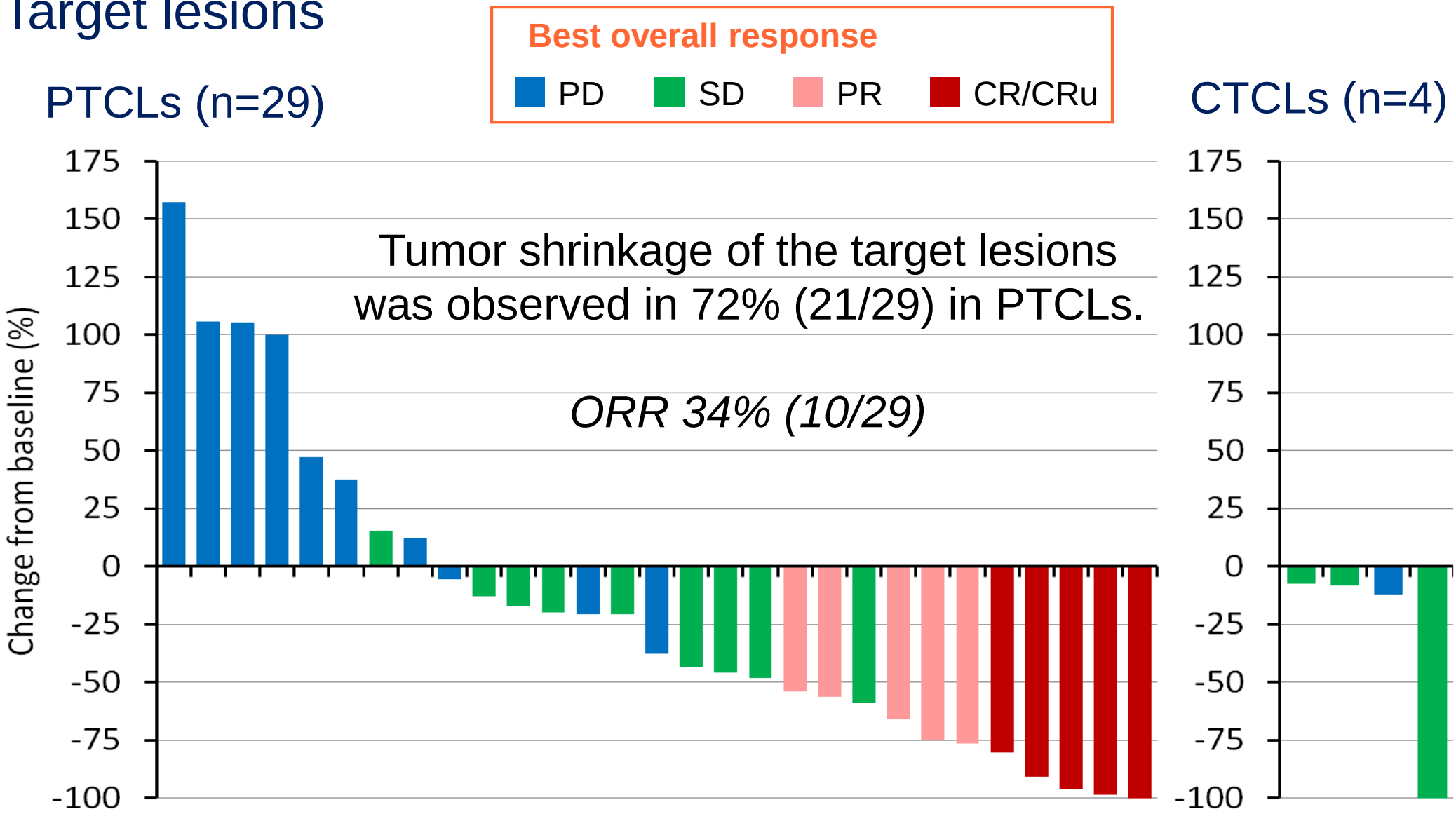
In another phase II study for ATL, skin disorders were observed in 67% (18/27).

*Ogura M, Tobinai K, et al.: J Clin Oncol 2014;32:1157-63*

# Phase II Study of Mogamulizumab for PTCL/CTCL: An Ancillary Study

(Tobinai K, et al.: T-Cell Lymphoma Forum, 2015)

## Target lesions



# Phase II Study of Mogamulizumab for PTCL/CTCL

- **35% of ORR** (13/37; 95% CI, 20 - 53%) **met the primary endpoint** defined as the best ORR (Threshold; 5%, Expected; 25%).
- Median PFS was 3.0 months.
- Median duration of response (DOR) and time to response (TTR) for PTCL responders (n=10) were 6.4 and 1.9 months, respectively.
- **Most common AEs were skin disorders,** acute infusion reaction, pyrexia and hematologic toxicities.

**Mogamulizumab is an effective agent with acceptable toxicities for relapsed PTCL & CTCL, leading to its approval in Japan in 2014.**

*Ogura M, Tobinai K, et al: J Clin Oncol 2014;32:1157-63 / Tobinai K, et al.: TCLF 2015*

# European Phase II Study of Mogamulizumab in Previously Treated PTCL

| **Best OR by Subtype** | **No of subjects** | **CR/PR n (%)** | **SD n (%)** | **>SD n (%)** |
|---|---|---|---|---|
| PTCL-NOS | 15 | 2* (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 |
| **Evaluable Subjects** | **35** | **4 (11%)** | **12 (34%)** | **16 (46%)** |

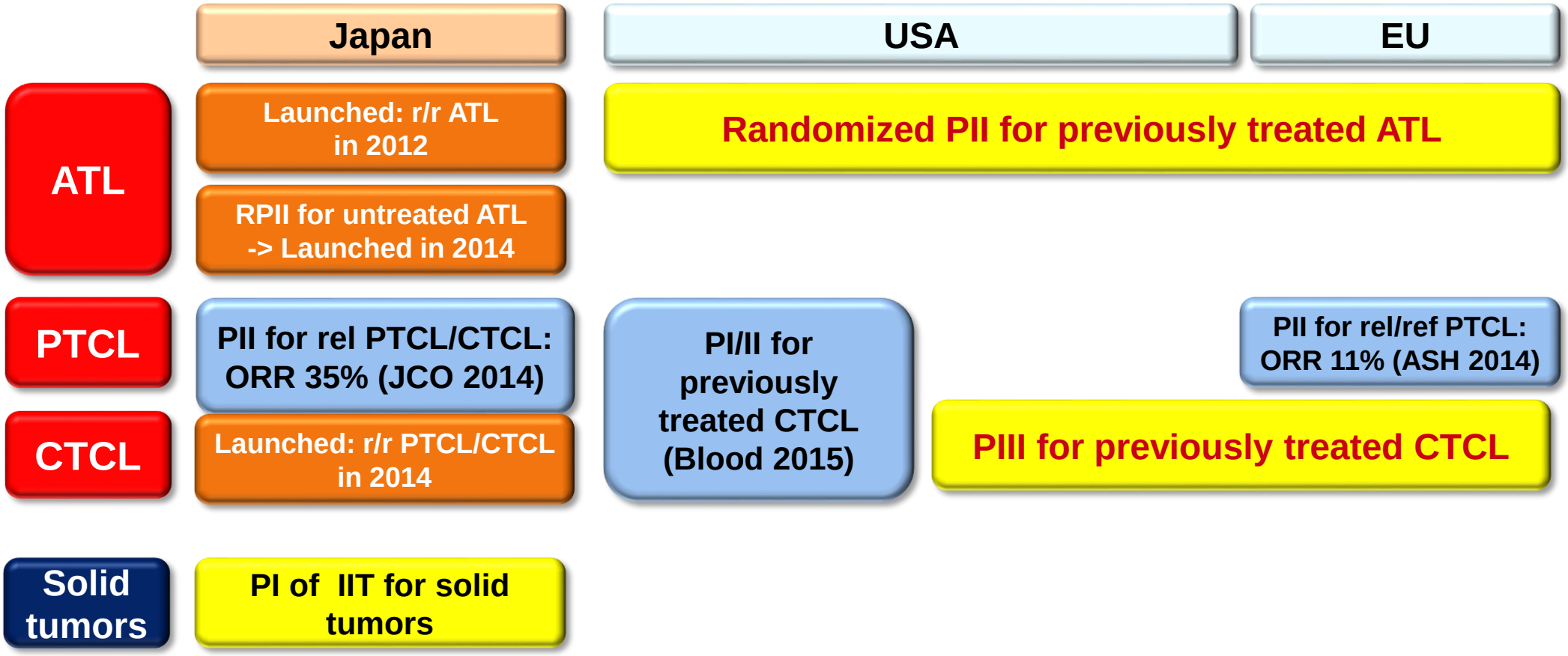
The median PFS was 2.1 months; similar results to the Japanese phase II study.

**The differences in ORRs between 2 studies (35% vs 11%) are partly due to the differences in patient population, including relapsed pts (100% vs 49%) and PS 2 (3% vs 39%).**

*Zinzani PL, et al.: Blood, Dec 2014;124:1763 (ASH 2014)*

# Worldwide Development Status of Mogamulizumab

(as of April 2015)




IIT: Investigator-initiated trial

Status: Launched | Completed | Ongoing | In preparation

*Courtesy of Kyowa-Kirin*

# Acknowledgments


## Investigators

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

## Flow Cytometry

Junichi Tsukada
Kouichi Nakata

## Immunohistochemistry

Shigeo Nakamura
Hiroshi Inagaki
Kouichi Ohshima

## Safety Review Committee

Kuniaki Itoh
Noriko Usui
Hirokazu Nagai

## Efficacy Review Committee

Junji Suzumiya
Takashi Terauchi
Ukihide Tateishi

## Expert Dermatologist

Tetsuo Nagatani
Akimichi Morita

## Expert Oncologist

Kazuo Tamura
Ryuzo Ueda

## Study Chairman

Masao Tomonaga

## Kyowa Hakko Kirin

Shiro Akinaga

**Sponsored by**

KYOWA KIRIN

**We would like to thank the patients who participated in this study and their families, as well as CRCs, study coordinators, and operation staffs.**