1) Adult T-cell Leukemia-lymphoma: Mogamulizumab inside the T-cell family

Kunihiro Tsukasaki, M.D., Ph.D.
Department of Hematology
National Cancer Center Hospital East
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.
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
Adult T-cell leukemia–lymphoma (ATL)

- Mature T-cell malignancy of Th2/Treg origin associated with HTLV-1
- Several tens millions of HTLV-1 carriers in the world, endemic in south-west coast of Japan, mid-and south-America and Africa
- About 5% of HTLV-1 carriers develop ATL during their life time
- Clinical feature is diverse and treatment strategy is based on subtype classification

<table>
<thead>
<tr>
<th>Clinical subtype</th>
<th>Smoldering/Chronic</th>
<th>Acute/Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ involvement</td>
<td>No/Minimum (skin etc)</td>
<td>Yes</td>
</tr>
<tr>
<td>LDH level</td>
<td>Normal or raised=&lt;x2</td>
<td>Raised&gt;x2</td>
</tr>
<tr>
<td>Calcium level</td>
<td>Normal</td>
<td>Raised</td>
</tr>
<tr>
<td>Median survival time</td>
<td>&gt; 24months</td>
<td>6-10 months</td>
</tr>
</tbody>
</table>

International peripheral T-cell and NK/T-cell lymphoma study: pathology findings and clinical outcomes on 1314 cases.
**P-Ⅲ study of VCAP-AMP-VECP vs. CHOP-14 in aggressive ATL:JCOG9801**

VCAP-AMP-VECP is a more effective regimen at the expense of higher toxicities, providing the basis for future investigations in the treatment of ATL.

**Randomization**
- Stratification: Institution, PS (0,1/2-4)

**Comparison**
- **CHOP-14**
  - x 8 cycles with G-CSF and IT x 3 of Ara-C, MTX and PSL

- **VCAP→AMP→VECP**
  - x 6 cycles with G-CSF and IT x 3 of Ara-C, MTX and PSL

**Results**
- MST=13M 3yr%OS=24% (VCAP-AMP-VECP, n=57)
- MST=11M 3yr%OS=13% (Bi-CHOP, n=61)

**Hazard ratio** = 0.75 (95% CI: 0.50–1.13) one-sided p=0.085 (0.029 after adjustment of charact. at reg.)

CR rate
- 40%
- 25%
- p=0.02

Recommended strategy for consideration on the treatment of ATL

Diagnosis of ATL

αHTLV-1 Ab positive PTCL

Subtype- classification

Indolent ATL
Smoldering/
Favorable Chronic ATL

Aggressive ATL
Acute/Lymphoma/
Unfavorable Chronic ATL

Watchful waiting/
IFN/AZT

VCAP-AMP-VECP
IFN/AZT (exclude Lymphoma type)
Allo-HSCT including RIST
Salvage therapy with new agents

ATL consensus Report; Drs from Brazil, France, Lebanon, Japan, UK and USA; JCO2009
Humanized anti-CCR4 mAb-induced ADCC activity against ATL cells obtained from patients tested in an autologous setting.

**Target**: Whole blood of refractory ATL patients

**Effector**: Non-ATL cell subset

**ATL Cell Subset**
- CD4
- CD25
- CCR4

**Non-ATL Cell Subset**
- CD4
- CD25
- CCR4

**Separation** (using CD3 mAb)

**Autologous ADCC**

**Graph**
- X-axis: CCR4 mAb (μg/mL)
- Y-axis: % ATL cell lysis
- Data points at 0, 0.1, 1.0, and 10 μg/mL

Ishida et al, Clin Cancer Res 2004;10:7529
P-I study of Mogamulizumab, a defucosylated anti-CCR4 Ab, in relapsed pts with ATL or peripheral T-cell lymphoma (PTCL)

Concept
A therapeutic antibody which binds to a chemokine receptor, CCR4, eliminates the target cells expressing CCR4 protein through a cytolyltic 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 2010
Phase II study of Mogamulizumab in relapsed ATL

A multicenter open labeled study

Relapsed ATL → CCR4 assessment with FCM / IHC → Registration

CCR4+ → Mogamulizumab 1.0 mg/kg/day (iv) weekly x 8

Primary endpoint; Overall response rate

Dosing and assessment schedule

Mogamulizumab, 1.0 mg/kg

D1 8 15 22 29 36 43 50 2 mos

Efficacy assessment
Pharmacokinetics:

P2 study of Mogamulizumab in relapsed aggressive ATL

**PK parameters** (After 8\textsuperscript{th} infusion)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ ($\mu\text{g/mL}$)</td>
<td>$42.9 \pm 14.2$</td>
</tr>
<tr>
<td>$C_{\text{trough}}$ ($\mu\text{g/mL}$)</td>
<td>$33.6 \pm 10.6$</td>
</tr>
<tr>
<td>$\text{AUC}_{0-7\text{days}}$ ($\mu\text{g} \cdot \text{h/mL}$)</td>
<td>$6297 \pm 1812$</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>$422 \pm 147$</td>
</tr>
</tbody>
</table>

No anti-Mogamulizumab antibody was detected in all pts

Ishida T, Tsukasaki K, Tobinai K, et al. JCO 2012

Ishida et al, Clin Cancer Res 2010
### Adverse events (n=27)*

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

<table>
<thead>
<tr>
<th>Non-Hematologic AEs</th>
<th>Grade</th>
<th>All grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute infusion reaction</td>
<td>1 0</td>
<td>24</td>
</tr>
<tr>
<td>Rash</td>
<td>5 0</td>
<td>17</td>
</tr>
<tr>
<td>ALT</td>
<td>2 0</td>
<td>11</td>
</tr>
<tr>
<td>AST</td>
<td>2 0</td>
<td>10</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>3 0</td>
<td>5</td>
</tr>
<tr>
<td>γ-GTP</td>
<td>3 0</td>
<td>4</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 0</td>
<td>4</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>2 0</td>
<td>3</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>0 1</td>
<td>3</td>
</tr>
<tr>
<td>Erythema multiforme**</td>
<td>1 0</td>
<td>1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1 0</td>
<td>1</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>1 0</td>
<td>1</td>
</tr>
<tr>
<td>Metabolic/Lab-other (LDH etc.)</td>
<td>3 0</td>
<td>14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hematologic AEs</th>
<th>Grade</th>
<th>All grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphopenia***</td>
<td>9 11</td>
<td>26</td>
</tr>
<tr>
<td>Leukocytopenia</td>
<td>8 0</td>
<td>18</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3 2</td>
<td>14</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5 0</td>
<td>14</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>1 0</td>
<td>8</td>
</tr>
</tbody>
</table>

CTCAEv3.0
* Possibly/probably/definitely drug-related
** Stevens-Johnson syndrome
*** Includes abnormal lymphocytes

Ishida T, Tsukasaki K, Tobinai K, et al. JCO 2012
# Efficacy assessment*

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

<table>
<thead>
<tr>
<th>Disease site</th>
<th>n</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>NE</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥ PR (%) [95% CI]</td>
</tr>
<tr>
<td>Blood</td>
<td>13</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>13 (100 %) -</td>
</tr>
<tr>
<td>Skin</td>
<td>8</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>5 (63 %) [25-92]</td>
</tr>
<tr>
<td>Nodal &amp; extranodal</td>
<td>12</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>3 (25 %) [6-57]</td>
</tr>
<tr>
<td>Overall**</td>
<td>26</td>
<td>8</td>
<td>5</td>
<td>2</td>
<td>11</td>
<td>0</td>
<td>13 (50 %) [30-70]</td>
</tr>
</tbody>
</table>

* 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, Tobinai K, et al. JCO 2012
# Efficacy assessment*

## P-2 study of Mogamulizumab in relapsed aggressive ATL

<table>
<thead>
<tr>
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<th>n</th>
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<th>SD</th>
<th>PD</th>
<th>NE</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>13</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>13 (100%)</td>
</tr>
<tr>
<td>Skin</td>
<td>8</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>5 (63%) [25-92]</td>
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<tr>
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<td>3</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>3 (25%) [6-57]</td>
</tr>
</tbody>
</table>

| 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**

**| 1st line CTx (mLSG15 + mLSG19) for aggressive ATL in the JCOG 9801 study #**

<table>
<thead>
<tr>
<th></th>
<th>Lymphoma</th>
<th>Acute</th>
<th>Unfavorable chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (# of all pts)</td>
<td>54% (14/26)</td>
<td>27% (22/81)</td>
<td>18% (2/11)</td>
</tr>
<tr>
<td>(95%CI)</td>
<td>(33-73%)</td>
<td>(18-38%)</td>
<td>(8-52%)</td>
</tr>
</tbody>
</table>

Conclusions:
PII study of Mogamulizumab in relapsed aggressive ATL

- 26 of 27 pts received 1.0 mg/kg of Mogamulizumab were evaluable for efficacy analysis.
- 50% of ORR (13/26; 95% CI, 30 - 70) met the primary endpoint defined as the best overall response (Threshold; 5%, Expected; 30%).
- Most common 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.
- Pharmacokinetic analysis showed that the concentrations sufficient to exert ADCC against ATL could be clinically achieved.
- No anti-Mogamulizumab antibody was detected in all pts.

Mogamulizumab is an effective agent with acceptable toxicity profiles for pts with relapsed aggressive ATL.

Ishida T, Tsukasaki K, Tobinai K, et al. JCO 2012
Dose-intensified chemotherapy alone or in combination with mogamulizumab in newly diagnosed aggressive ATL: a randomized phase II study

1:1 Randomization

- **1st stratification factor:**
  - Disease subtype:
    - Acute, lymphoma, or unfavorable chronic

- **2nd stratification factor:**
  - Age (<56 or ≥ 56)

**Open-label design**

- **VCAP-AMP-VECP arm**
  - (mLSG15 × 4cycles)

- **VCAP-AMP-VECP + Mogamulizumab arm**
  - (mLSG15 × 4cycles + Mogamulizumab: every 2 weeks x 8)

**Primary end point;**
- %CR

**Secondary end points;**
- ORR, PFS, OS, safety

Ishida T, Tobinai K, et al. BJH 2015
Patients Characteristics: Chemo. alone vs. Chemo.+ mogamulizumab: a randomized phase II study

<table>
<thead>
<tr>
<th></th>
<th>mLSG15 + mogamulizumab (n = 29)</th>
<th>mLSG15 (n = 24)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATL subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>20 (69%)</td>
<td>17 (71%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>6 (21%)</td>
<td>7 (29%)</td>
</tr>
<tr>
<td>Unfavorable chronic</td>
<td>3 (10%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Age, year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>61</td>
<td>64</td>
</tr>
<tr>
<td>Range</td>
<td>49-81</td>
<td>37-74</td>
</tr>
<tr>
<td>&lt;56</td>
<td>11 (38%)</td>
<td>6 (25%)</td>
</tr>
<tr>
<td>&gt;=56</td>
<td>18 (62%)</td>
<td>18 (75%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (41%)</td>
<td>16 (67%)</td>
</tr>
<tr>
<td>Female</td>
<td>17 (59%)</td>
<td>8 (33%)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>16 (55%)</td>
<td>13 (54%)</td>
</tr>
<tr>
<td>1</td>
<td>10 (35%)</td>
<td>9 (38%)</td>
</tr>
<tr>
<td>2</td>
<td>3 (10%)</td>
<td>2 (8%)</td>
</tr>
</tbody>
</table>

Ishida T, Tobinai K, et al. BJH 2015
Adverse Events
Chemo. alone vs. Chemo.+ mogamulizmab: a randomized phase II study

<table>
<thead>
<tr>
<th>AEs (CTCAE v4.0)</th>
<th>mLSG15 + Mogamulizumab (n=29)</th>
<th>mLSG15 (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Term</td>
<td>All Grades</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>97%</td>
<td>97%</td>
</tr>
<tr>
<td>Anemia</td>
<td>97%</td>
<td>97%</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>90%</td>
<td>90%</td>
</tr>
</tbody>
</table>

Ishida T, Tobinai K, et al. BJH 2015
### Response and Survival

Chemo. alone vs. Chemo.+ mogamulizumab: a randomized phase II study

<table>
<thead>
<tr>
<th></th>
<th>mLSG15 + Mogamulizumab (n=29)</th>
<th>mLSG15 (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>CRu</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>PR</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>CR rate (95%CI)</td>
<td>52% (33-71)</td>
<td>33% (16-55)</td>
</tr>
<tr>
<td>ORR (95%CI)</td>
<td>86% (68-96)</td>
<td>75% (53-90)</td>
</tr>
</tbody>
</table>

**MST**

- mLSG15: 8.5m
- mLSG15 + Mogamulizumab: 6.3m

Ishida T, Tobinai K, et al. BJH 2015
<table>
<thead>
<tr>
<th>Cohort</th>
<th>Patient ID</th>
<th>Age, years</th>
<th>Diagnosis</th>
<th>Number of Prior Treatments</th>
<th>Treatment Duration, days</th>
<th>Best Overall Response</th>
<th>TTR, days</th>
<th>DOR, days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>0021001</td>
<td>69</td>
<td>PTCL-NOS</td>
<td>1</td>
<td>21</td>
<td>PD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0011002</td>
<td>64</td>
<td>ATL-acute</td>
<td>2</td>
<td>637</td>
<td>PR</td>
<td>57</td>
<td>505</td>
</tr>
<tr>
<td></td>
<td>0041003</td>
<td>69</td>
<td>ATL-unfavorable chronic</td>
<td>1</td>
<td>103</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 2</td>
<td>0022001</td>
<td>42</td>
<td>PTCL-NOS</td>
<td>1</td>
<td>387</td>
<td>PR</td>
<td>106</td>
<td>282</td>
</tr>
<tr>
<td></td>
<td>0032003</td>
<td>74</td>
<td>ATL-lymphoma</td>
<td>1</td>
<td>37</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0022004</td>
<td>61</td>
<td>ATL-acute</td>
<td>2</td>
<td>138</td>
<td>PR</td>
<td>55</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>0042005</td>
<td>32</td>
<td>ALCL</td>
<td>11</td>
<td>56</td>
<td>PD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0032006</td>
<td>69</td>
<td>ATL-acute</td>
<td>1</td>
<td>66</td>
<td>PD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0022007</td>
<td>61</td>
<td>ATL-acute</td>
<td>2</td>
<td>&gt; 28*</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 3</td>
<td>0063001</td>
<td>71</td>
<td>ATL-acute</td>
<td>3</td>
<td>24</td>
<td>PD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0013002</td>
<td>53</td>
<td>PTCL-NOS</td>
<td>1</td>
<td>71</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0043003</td>
<td>60</td>
<td>ATL-unfavorable chronic</td>
<td>1</td>
<td>&gt; 323*</td>
<td>PR</td>
<td>54</td>
<td>&gt; 279*</td>
</tr>
<tr>
<td></td>
<td>0053004</td>
<td>69</td>
<td>ATL-acute</td>
<td>1</td>
<td>25</td>
<td>PD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Best Overall Response Rate**: 31% (4/13, All patients), 33% (3/9, ATL patients)

Uike N, Tsukasaki K, Toninai K, et al. ASH 2012
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
- IFNa + AZT vs. Watchful waiting, or Mogamulizmab? for Indolent-ATL
- allo-HSCT for aggressive ATL; RIST for aged patients
- Mogamulizmab alone, or combined with chemo/HSCT or other new agents for aggressive ATL
- new agents: HDACI, ImiDs, Folate, Purine analogs, Mo Abs
- Grouping with other PTCLs; i.e. Brentuximab vedotin P3 trial
Acknowledgment: Mogamulizmab Study for ATL in Japan

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