First International, Randomized Phase 3 Study in Patients With Relapsed/Refractory (R/R) Peripheral T-cell Lymphoma (PTCL): Alisertib (MLN8237) Versus Investigator's Choice (Lumiere Trial; NCT01482962)

Owen A. O'Connor,1 Muhit Özcan,2 Eric D. Jacobsen,3 Josep Maria Roncero Vidal,4 Judith Trotman,5 Judit Demeter,6 Tamás Masszi,7 Juliana Pereira,8 Radhakrishnan Ramchandren,9 Francesco A. d'Amore,10 Francine Foss,11 Won-Seog Kim,12 John P. Leonard,13 Carlos Sérgio Chiattone,14 Pier Luigi Zinzani,15 Hua Liu,16 JungAh Jung,17 Xiaofei Zhou,17 E. Jane Leonard,17 Claudio Dansky Ullmann,16 and Andrei R. Shustov18

1Center for Lymphoid Malignancies, Columbia University Medical Center, New York Presbyterian Hospital, New York, NY; 2Ankara University Medical School, Cebeci Hospital, Dikimevi, Ankara, Turkey; 3Dana-Farber Cancer Institute, Boston, MA; 4Catalan Institute of Oncology, Girona, France; 5Concord Repatriation General Hospital, University of Sydney, Concord, Australia; 6Semmelweis University, Budapest, Hungary; 7St. Istvan and St. Laszlo Hospital, Budapest, Hungary; 8Medical School of Sao Paulo University, Sao Paulo, Brazil; 9Karmanos Cancer Institute, Detroit, MI; 10Aarhus University Hospital, Aarhus, Denmark; 11Smilow Cancer Hospital at Yale-New Haven, New Haven, CT; 12Samsung Medical Center, Seoul, South Korea; 13Weill Cornell Medical College, New York, NY; 14Santa Casa Medical School, Sao Paulo, Brazil; 15Institute of Hematology “L. e A. Seràgnoli”, University of Bologna, Bologna, Italy; 16Formerly Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; 17Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; 18University of Washington Medical Center – Seattle Cancer Care Alliance & Fred Hutchinson Cancer Research Center, Seattle, WA
BACKGROUND AND RATIONALE

- **PTCLs:** Rare, aggressive, heterogeneous group of NHLs for which outcomes remain poor

- **Alisertib:** Investigational, oral, selective inhibitor of Aurora A kinase, a key mitotic regulator overexpressed or amplified in various cancers

- **Preclinical findings:** Antitumor activity of alisertib as a single agent and synergistic partner in combination therapies

- **Phase 2 data:** Support antitumor activity and favorable tolerability for single-agent alisertib in R/R NHL and PTCL
  - ORR of 27% in R/R NHL and 30% in R/R PTCL subtypes

AAK, Aurora A kinase; NHL, non-Hodgkin lymphoma; ORR overall response rate; PTCL, peripheral T-cell lymphoma; R/R, relapsed/refractory

5. Zullo KM, et al. CCR 2015; 21 (18); 4097–4109

Presentation at the 57th ASH Annual Meeting and Exposition on December 6, 2015.
LUMIERE STUDY (NCT01482962)

- International, multicenter, randomized, open-label phase 3 trial to evaluate the efficacy and safety of single-agent alisertib versus investigator's choice (pralatrexate, gemcitabine, or romidepsin) in patients with R/R PTCL

- First initiated randomized trial in this setting

- 166 sites participated across 27 countries
  - Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Mexico, Netherlands, New Zealand, Peru, Poland, Portugal, Puerto Rico, Romania, Russian Federation, Spain, Sweden, Turkey, United Kingdom, United States of America
**LUMIERE STUDY DESIGN**

**Eligibility**
- Age ≥18 years
- R/R PTCL (WHO criteria) after ≥1 prior conventional systemic cytotoxic therapy
- Measurable disease (2007 IWG criteria)
- Tumor biopsy for central review
- ECOG PS 0–2
- No prior treatment with study drugs

**Randomization 1:1***

**Arm A: Alisertib**
- 50 mg BID ECT
- Days 1–7; 21-day cycles

**Arm B: Single-agent comparator (investigator choice) †**

**Pralatrexate**
- 30 mg/m² via IV push (3–5 minutes)
- Once weekly for 6 weeks; 7-week cycles
- Vitamin B12 + folic acid supplements

**Gemcitabine (currently not approved for use in hematologic malignancy)**
- 1000 mg/m² via IV over 30 minutes
- Days 1, 8, and 15; 28-day cycles

**Romidepsin**
- 14 mg/m² via IV infusion over 4 hours
- Days 1, 8, and 15; 28-day cycles

**Treatment until disease progression or unacceptable toxicity**
(Patients achieving ≥SD could continue treatment for up to 2 years)

**Primary:**
- ORR (CR+PR)
- PFS (IRC)

**Secondary:**
- OS (key)
- CR rate
- DOR
- Safety

***Stratified by:***
- Nodal vs extranodal disease
- IPI score (0/1/2 vs 3/4/5)
- Region (North America + EU vs Rest of World)

†Crossover to alisertib after comparator arm was not permitted.

BID, twice daily; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ECT, enteric-coated tablet; IPI, International Prognostic Index; IRC, independent review committee; IV, intravenous; IWG, International Working Group; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; WHO, World Health Organisation

Presentation at the 57th ASH Annual Meeting and Exposition on December 6, 2015.
Adaptive sample size reassessment approach, with two interim analyses, plus planned final analysis

First Futility Interim Analysis (IA1)

ORR (N=74)

Stop for futility

Second Interim Analysis (IA2)

ORR (N=146)

PFS

CP ≥ 85%

43% ≤ CP < 85%

3% < CP ≤ 43%

CP ≤ 3%

Stop for futility

Final Analysis

PFS

Planned E=201

PFS

E increased ≤261 pre-specified

PFS

Planned E=201

ORR*

IA2 results indicated a low probability of claiming superiority of alisertib for PFS at the final analysis

- Per IDMC recommendation, enrollment was stopped at 271 patients

CP, conditional power; E, number of PFS events; IDMC, Independent Data Monitoring Committee; N, number of patients who are response-evaluable

* ORR will be tested at the final analysis if the test of ORR is not significant at IA2 and the test of PFS is significant at the final analysis.

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ASSESSMENTS

- Sample size provided:
  - 80% power to detect the difference in ORR (55% alisertib vs 30% comparator) at IA2
  - ~85% power to detect a 37.5% reduction in PFS HR in favor of alisertib at final analysis

- Efficacy was evaluated according to IWG criteria (2007)
  - Response was assessed by central imaging (IRC)
  - Efficacy was assessed every 8 weeks until week 40, and every 12 weeks thereafter

- PTCL disease subtype was confirmed by Central Review (Cleveland Clinic)

- AEs were graded by NCI-CTCAE v4.0

- Data are reported from final data cut (30 June 2015)

AEs, adverse events; HR, hazard ratio; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events
# Demographics and Baseline Characteristics (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Alisertib n=138</th>
<th>Comparator n=133*</th>
<th>Total N=271</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>63 (19–82)</td>
<td>63 (27–86)</td>
<td>63 (19–86)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>92 (67)</td>
<td>86 (65)</td>
<td>178 (66)</td>
</tr>
<tr>
<td><strong>Ann Arbor stage III/IV, n (%)</strong></td>
<td>123 (89)</td>
<td>115 (86)</td>
<td>238 (88)</td>
</tr>
<tr>
<td><strong>BM involvement, n (%)†</strong></td>
<td>37 (27)</td>
<td>44 (33)</td>
<td>81 (30)</td>
</tr>
<tr>
<td><strong>Extranodal involvement, n (%)†</strong></td>
<td>78 (57)</td>
<td>76 (57)</td>
<td>154 (57)</td>
</tr>
<tr>
<td><strong>IPI score, n (%)‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Int/high (3–5)</td>
<td>63 (46)</td>
<td>70 (53)</td>
<td>133 (49)</td>
</tr>
<tr>
<td><strong>Median LDH, U/L (range)</strong></td>
<td>235 (122–2283)</td>
<td>238 (111–1935)</td>
<td>238 (111–2283)</td>
</tr>
<tr>
<td><strong>Median lines of prior therapy, n (range)</strong></td>
<td>2 (1–11)</td>
<td>2 (1–9)</td>
<td>2 (1–11)</td>
</tr>
</tbody>
</table>

*Pralatrexate (n=80), gemcitabine (n=30), or romidepsin (n=23); †At study entry; ‡Investigator assessed

BM, bone marrow; int, intermediate; ITT, intention to treat; LDH, lactate dehydrogenase

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## DISEASE SUBTYPES (ITT)

<table>
<thead>
<tr>
<th>Central Review, n (%)</th>
<th>Alisertib n=138</th>
<th>Comparator n=133</th>
<th>Total N=271</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCL-NOS</td>
<td>62 (45)</td>
<td>56 (42)</td>
<td>118 (44)</td>
</tr>
<tr>
<td>AITL</td>
<td>31 (22)</td>
<td>30 (23)</td>
<td>61 (23)</td>
</tr>
<tr>
<td>ALCL, ALK-</td>
<td>7 (5)</td>
<td>10 (8)</td>
<td>17 (6)</td>
</tr>
<tr>
<td>ALCL, ALK+</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Enteropathy-type TCL</td>
<td>3 (2)</td>
<td>3 (2)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Extranodal T-/NK-cell lymphoma, nasal type</td>
<td>2 (1)</td>
<td>2 (2)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Subcutaneous Panniculitis-like TCL</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Transformed Mycosis Fungoides</td>
<td>8 (6)</td>
<td>8 (6)</td>
<td>16 (6)</td>
</tr>
<tr>
<td>Other</td>
<td>22 (16)</td>
<td>18 (14)</td>
<td>40 (15)</td>
</tr>
<tr>
<td>No tumor tissue submitted</td>
<td>2 (1)</td>
<td>4 (3)</td>
<td>6 (2)</td>
</tr>
</tbody>
</table>

AITL, angioimmunoblastic TCL; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; NOS, not otherwise specified; TCL, T-cell lymphoma

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**BEST OVERALL RESPONSE RATE***

ORR (Alisertib vs Comparator): 35% vs 46%
Odds Ratio 0.65 (95% CI: 0.36, 1.18) p=0.077

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Alisertib (n=96)</th>
<th>All (n=85)</th>
<th>Pralatrexate (n=45)</th>
<th>Gemcitabine (n=22)</th>
<th>Romidepsin (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (CR + PR)</td>
<td>34 (35)</td>
<td>39 (46)</td>
<td>20 (44)</td>
<td>8 (36)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>CR</td>
<td>18 (19)</td>
<td>24 (28)</td>
<td>13 (29)</td>
<td>5 (23)</td>
<td>6 (33)</td>
</tr>
<tr>
<td>PR</td>
<td>16 (17)</td>
<td>15 (18)</td>
<td>7 (16)</td>
<td>3 (14)</td>
<td>5 (28)</td>
</tr>
<tr>
<td>SD</td>
<td>29 (30)</td>
<td>17 (20)</td>
<td>11 (24)</td>
<td>3 (14)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>PD</td>
<td>33 (34)</td>
<td>29 (34)</td>
<td>14 (31)</td>
<td>11 (50)</td>
<td>4 (22)</td>
</tr>
</tbody>
</table>

*Response-evaluable population, excluding tMF
CI, confidence interval; OR, odds ratio; PD, progressive disease; tMF, transformed mycosis fungoides

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PROGRESSION-FREE SURVIVAL BY IRC (ITT)

Alisertib vs Comparator:
Median PFS 115 vs 104 days
HR 0.87 (95% CI: 0.64, 1.16)
p=0.177

PFS is defined as the time from the date of randomization to the date of first documentation of PD or death due to any cause, whichever occurs first.
PROGRESSION-FREE SURVIVAL BY IRC (PP)

**Alisertib vs Comparator:**
Median PFS 120 vs 104 days
HR 0.82 (95% CI: 0.59, 1.14)
p=0.103

Survival probability

Survival time (days)

<table>
<thead>
<tr>
<th>Survival time (days)</th>
<th>0</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>240</th>
<th>300</th>
<th>360</th>
<th>420</th>
<th>480</th>
<th>540</th>
<th>600</th>
<th>660</th>
<th>720</th>
<th>780</th>
<th>840</th>
<th>900</th>
<th>960</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>108</td>
<td>56</td>
<td>29</td>
<td>20</td>
<td>14</td>
<td>7</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Censored</td>
<td>114</td>
<td>71</td>
<td>39</td>
<td>27</td>
<td>20</td>
<td>13</td>
<td>10</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

PP, per protocol

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OVERALL SURVIVAL (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Alisertib (n=138)</th>
<th>Comparator (n=133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, n (%)</td>
<td>75 (54)</td>
<td>75 (56)</td>
</tr>
<tr>
<td>Censored, n (%)</td>
<td>63 (46)</td>
<td>58 (44)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>13.6</td>
<td>12.1</td>
</tr>
<tr>
<td>2-year OS, %</td>
<td>35</td>
<td>35</td>
</tr>
</tbody>
</table>

Alisertib vs Comparator: HR 0.96 (95% CI: 0.70, 1.33) p=0.338

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## SAFETY OVERVIEW*

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Alisertib n=137</th>
<th>Comparator n=127†</th>
<th>Total N=264</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>136 (99)</td>
<td>126 (99)</td>
<td>262 (99)</td>
</tr>
<tr>
<td>Drug-related AE</td>
<td>121 (88)</td>
<td>119 (94)</td>
<td>240 (91)</td>
</tr>
<tr>
<td>Grade ≥3 AE</td>
<td>116 (85)</td>
<td>100 (79)</td>
<td>216 (82)</td>
</tr>
<tr>
<td>Drug-related grade ≥3 AE</td>
<td>96 (70)</td>
<td>86 (68)</td>
<td>182 (69)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>75 (55)</td>
<td>69 (54)</td>
<td>144 (55)</td>
</tr>
<tr>
<td>Drug-related serious AE</td>
<td>47 (34)</td>
<td>41 (32)</td>
<td>88 (33)</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>13 (9)</td>
<td>18 (14)</td>
<td>31 (12)</td>
</tr>
<tr>
<td>On-study deaths</td>
<td>11 (8)</td>
<td>15 (12)</td>
<td>26 (10)</td>
</tr>
</tbody>
</table>

*Safety population; †Pralatrexate (n=76), gemcitabine (n=29), or romidepsin (n=22)
SAFETY

Most common AEs (≥25% in either arm), %*

- Anemia
- Neutropenia
- Diarrhea
- Thrombocytopenia
- Fatigue
- Pyrexia
- Stomatitis
- Alopecia
- Leukopenia
- Nausea

*Safety population (alisertib, n=137: comparator, n=127)
SAFETY (CONT’D)

Most common grade ≥3 AEs (≥10% in either arm), %*

- Neutropenia
- Anemia
- Thrombocytopenia
- Leukopenia
- Febrile neutropenia
- ANC decreased
- WBC decreased
- Stomatitis

*Safety population (alisertib, n=137: comparator, n=127)
ANC, absolute neutrophil count; WBC, white blood cell

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SUMMARY

- First randomized study in the R/R PTCL setting

- Single-agent alisertib showed activity in R/R PTCL, but was not superior to the comparator arm

- Tolerability of alisertib was similar to comparators

- Patients deriving benefit continue on treatment

- Exploratory analyses evaluating potential response biomarkers are ongoing
With thanks to the patients who participated in this study, and their families

We also thank the physicians, research nurses, study coordinators, and research staff

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