Information Meeting on ALECENSA®

CHUGAI PHARMACEUTICAL CO., LTD.
August 21, 2014

Although this presentation includes information regarding pharmaceuticals (including products under development), the information is not intended as any advertisement and/or medical advice.
Forward-Looking Statements

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the “Company”). These statements reflect the Company’s current analysis of existing information and trends. Actual results may differ from expectations based on risks and uncertainties that may affect the Company’s businesses.
Overview of ALECENSA®

Megumi UZU
ALECENSA Lifecycle Leader
Chugai Pharmaceutical Co., Ltd.
Outline of ALECENSA®

ALECENSA® is created by Chugai Pharmaceutical Co., Ltd. as selective ALK inhibitor with benzo[b]carbazole structure.

Development code: AF802

Compound number: CH5424802/RO5424802

Nonproprietary name: Alectinib hydrochloride (JAN)

Molecular weight: 519.08

Chemical name: 9-Ethyl-6, 6-dimethyl-8-[4-(morpholin-4-yl)piperidin-1-yl]-11-oxo-6, 11-dihydro-5H-benzo[b]carbazole-3carbonitrile hydrochloride

Structure: Selective ALK inhibitor with benzo[b]carbazole structure

Target: Human Anaplastic Lymphoma Kinase (ALK)
Development History of ALECENSA® (Alectinib)

- EML4-ALK has been identified in NSCLC
- crizotinib approved in U.S.
- crizotinib approved in Japan
- ceritinib approved in U.S. (crizotinib failure)
- License agreement with Roche (Oct.2012)
- Breakthrough Therapy Designation by FDA (Jun.2013)
- Orphan Drug Designation in Japan (Sep.13.2013)
- Application for approval in Japan (Oct.7.2013)
- Approval in Japan (Jul.4.2014)
- Phase I/II (AF-001JP) Chemo pretreated/ALK-TKI naïve
- Bioequivalence study of 150 mg capsule and 20/40 mg capsule
- BE study (JP28297)
- Phase III (JO28928/J-ALEX study) 1L/2L ALK-TKI naïve alectinib vs crizotinib

ALK Inhibitor Screening and Derivatization to ALECENSA®

1. Compound library
   - High-throughput kinase inhibitor screening
   - KARPAS-299 (NPM-ALK) mouse xenograft model (po, qd x11)

   **Hit A**
   **Hit B**
   **Hit C**
   ... 

   Lead compound

   Improvement of ALK inhibitory activity, kinase selectivity, & PK profiles, etc.

2. Ultra high-throughput screening with a library of more than one million compounds

   Identify a more unique and potent lead compound with tetracyclic structure.

<table>
<thead>
<tr>
<th>ED&lt;sub&gt;50&lt;/sub&gt;</th>
<th>MTD/ED&lt;sub&gt;50&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 mg/kg</td>
<td>2.9-fold</td>
</tr>
<tr>
<td>0.81 mg/kg</td>
<td>&gt;75-fold</td>
</tr>
</tbody>
</table>

   CH5424802

   Synthesize almost 600 derivatives

   ED<sub>50</sub>; effective dose causing 50% inhibition
   MTD; maximum tolerated dose

   ALECENSA®
Kinase Inhibitory Profile of ALECENSA®
(in vitro)

The Mechanism of Antitumor Activity of ALECENSA®

- Inhibition of proliferation
- Apoptosis

Description

Regulatory classification
Powerful drug, Prescription-only drug*
*Caution - Use only as directed by a physician.

Storage
ALECENSA® should be stored at room temperature.

Expiration date
2 years and 6 months
(Do not use after expiration date indicated on package and label.)

ALECENSA® Capsule 20 mg: 14 capsules (bottle)
ALECENSA® Capsule 40 mg: 98 capsules (bottle)

Formulation
Hard capsule (Size. 2)
Longer diameter:18mm
Shorter diameter:6mm
Weight: 320 mg
Identification code C-42C/20mg

Formulation
Hard capsule (Size. 2)
Longer diameter:18mm
Shorter diameter:6mm
Weight: 320 mg
Identification code C-42C/40mg
Indications

< INDICATIONS >

ALK fusion gene-positive unresectable, recurrent or advanced non-small cell lung cancer

< Precautions related to INDICATIONS >

1. ALECENSA® should be administered in patients with ALK fusion gene-positivity confirmed through testing by a test facility or pathologist with adequate experience. Testing should be performed using an approved in vitro diagnostic based on the principles of immunohistochemical staining and fluorescence in situ hybridization (see CLINICAL STUDIES).

2. Efficacy and safety of ALECENSA® in chemotherapy-naïve patients have not been established.

3. Efficacy and safety have not been established for postoperative adjuvant chemotherapy with ALECENSA®.

4. Careful consideration should be given to treatments other than ALECENSA® and eligible patients should be selected after closely reading the CLINICAL STUDIES section to gain a thorough understanding of the efficacy and safety of ALECENSA®.
Dosage and Administration

**< DOSAGE AND ADMINISTRATION >**

The usual adult dosage is 300 mg alectinib administered orally twice daily.

**< Precautions related to DOSAGE AND ADMINISTRATION >**

To prevent a food effect, it is recommended that ALECENSA® be administered in fasted patients, according to the specifications of the clinical studies (see PHARMACOKINETICS and CLINICAL STUDIES).
Conditions for Approval

1. A very limited number of patients participated in Japanese clinical studies. Therefore, drug use surveillance of all patients receiving ALECENSA® after launch should be conducted until data for a set number of patients have been accumulated. These data should be used to understand the background of patients using ALECENSA®, to collect early-phase safety and efficacy data on ALECENSA®, and to take any necessary measures for appropriate use of ALECENSA®.

2. The MAH* should take measures necessary to ensure that ALECENSA® is administered only under the supervision of a physician, medical institution, and supervising pharmacist experienced with diagnosis of and chemotherapy for lung cancer and capable of adequately managing the risks, etc., of ALECENSA® treatment.

* MAH :Marketing Authorization Holder
### Product Characteristics

<table>
<thead>
<tr>
<th>1</th>
<th>Japan originated ALK inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALECENSA® suppresses proliferation of ALK fusion gene-positive tumor cells by inhibiting ALK tyrosine kinase activity.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2</th>
<th>Efficacy in non-clinical studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALECENSA® inhibited cell growth of ALK fusion gene-positive human NSCLC cell line (NCI-H2228) (in vitro). An antiproliferative effect was shown in NCI-H228 human tumor mouse xenograft model.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3</th>
<th>Efficacy in Japanese Phase I/II study (AF-001JP)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In the Phase II part of AF-001JP study,</td>
</tr>
<tr>
<td></td>
<td>• The response rate was 93.5% (95% CI, 82.1-98.6). CR was 19.6%</td>
</tr>
<tr>
<td></td>
<td>• Median PFS was 27.7 months (95% CI: 26.9-not estimable)</td>
</tr>
<tr>
<td></td>
<td>• 2-year survival rate was 79% (95% CI: 63-89)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4</th>
<th>Safety in Japanese Phase I/II study (AF-001JP)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In the case which patients were treated with 300 mg twice daily in AF-001JP study.</td>
</tr>
<tr>
<td></td>
<td>• Treatment-related adverse events were observed in 56 patients (96.6%).</td>
</tr>
<tr>
<td></td>
<td>• The most common treatment-related adverse events included increased blood bilirubin, dysgeusia and rash, increased AST (GOT), and increased blood creatinine</td>
</tr>
<tr>
<td></td>
<td>• Clinically significant treatment-related adverse events included Interstitial lung disease, hepatic function disorder, decreased neutrophils, decreased white blood cells, gastrointestinal perforation, thromboembolism</td>
</tr>
</tbody>
</table>

modified from Product monograph
### Reference:
#### Ongoing Global Clinical Studies

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Patients</th>
<th>Phase</th>
<th>Dosage of Alectinib</th>
<th>Treatment arm</th>
<th>Primary Objective</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF002JG/ NP28761&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>ALK fusion gene-positive NSCLC Crizotinib failure (Phase I) Crizotinib failure and one or more Platinum based chemotherapy (Phase II)</td>
<td>Phase I/II</td>
<td>300-900mg b.i.d /p.o. (Phase I) 600mg or 900mg b.i.d /p.o. (Phase II)</td>
<td>- Alectinib</td>
<td>DLT (Phase I) RR (Phase II)</td>
<td>Phase I: 36 Phase II: 85</td>
</tr>
<tr>
<td>NP28673&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>ALK fusion gene-positive NSCLC Crizotinib failure Chemo naïve or one or more Platinum based chemotherapy</td>
<td>Phase II</td>
<td>600mg b.i.d /p.o.</td>
<td>- Alectinib (combination of erlotinib is offered after progression and patient harboring EGFR mutation)</td>
<td>DLT, RR, safety, pharmacokinetics, PFS, OS</td>
<td>130</td>
</tr>
<tr>
<td>ALEX&lt;sup&gt;2&lt;/sup&gt;</td>
<td>ALK fusion gene-positive NSCLC Treatment-naïve</td>
<td>Phase III</td>
<td>600mg b.i.d /p.o.</td>
<td>- Alectinib - Crizotinib</td>
<td>PFS</td>
<td>286</td>
</tr>
</tbody>
</table>

1) S.Gadgeel, et al. WCLC2013, O16.06  
2) ClinicalTrials.gov
Overview of ALK-Rearranged Non-Small Cell Lung Cancer and Clinical Trial of Alectinib (AF-001JP)

Yuichiro OHE, M.D.
Deputy Director, Chief,
Division of Thoracic Oncology
National Cancer Center Hospital, Japan
Death from Lung Cancer in Japan (2012)

- Male 51,372  Female 20,146
Histological Classification of Lung Cancer

- **SCLC** (Small Cell Lung Cancer)
  - Male: 15%, Female: 11%

- **NSCLC** (Non-Small Cell Lung Cancer)
  - Male: 85%, Female: 89%

- **Small Cell Carcinoma**
  - Male: 15%, Female: 11%

- **Squamous Cell Carcinoma**
  - Male: 32%, Female: 14%

- **Adenocarcinoma**
  - Male: 40%, Female: 63%

- **Large Cell Carcinoma**
  - Male: 5%, Female: 3%

- **Other**
  - Male: 8%, Female: 9%

Treatment Algorithm of Lung Cancer

Lung Cancer

Small Cell Lung Cancer
- Limited Disease (LD)
- Extensive Disease (ED)

Non-Small Cell Lung Cancer
- Resectable
  - Stage I: Surgery + CT
  - Stage II: CT
  - Stage IIIA/IIIB: CT + RT
- Un-Resectable
  - Stage IIIB: CT + RT
  - Stage IV: CT

CT: Chemo Therapy  RT: Radio Therapy  PCI: Prophylactic cranial irradiation

Rinsho Shyuyou Gaku, 3rd ed. Tokyo; Gan To Kagaku Ryoho Co. Ltd. 17
Lung Cancer Treatment Guideline (2014)

Treatment of Stage IV Non-Small Cell Lung Cancer

Stage IV Non-Small Cell Lung Cancer

Non-squamous

- EGFR Mutation
  - 1st line
  - Progression Disease
  - 2nd line+

- ALK-rearranged
  - 1st line
  - Progression Disease
  - 2nd line+

- EGFR / ALK Wild type or unknown
  - 1st line
  - Progression Disease
  - 2nd line+

Squamous

- EGFR / ALK testing is not required
  - 1st line
  - Progression Disease
  - 2nd line+

History of the Research of the ALK Gene in Various Cancers

ALK was identified in ALCL as NPM-ALK fusion gene 1

1994

EML4-ALK Fusion gene was reported in NSCLC 3

2000

VCL-ALK fusion gene in RMC 6

2007

ALK point mutation in ATC 5

2008

ALK gene amplification in NBL 4

2011

Crizotinib approved in Japan

2012

ALK gene amplification in RMS 7


ALK (anaplastic large cell lymphoma)
IMT (inflammatory myofibroblastic tumor)
NBL (neuroblastoma)
ATC (anaplastic thyroid cancer)
RMC (renal medullary carcinoma)
RMS (rhabdomyosarcoma)
EML4-ALK Rearranged

EML4-ALK is Activated even in the Absence of Binding of the Ligand

Mechanism of Alectinib

- Inhibition of proliferation
- Apoptosis

Backgrounds of Patients Harboring ALK Gene Rearrangements

- ALK rearranged Lung Cancer is found in about 4% of all cases of Non-Small Cell Lung Cancer

- ALK rearranged gene is frequently found in patients with following backgrounds
  - Adenocarcinoma
  - Wild type Epidermal Growth Factor Receptor
  - Younger generations
  - Never or light smokers
ALK Testing

Lung Cancer Specimen

- Cytology samples, frozen tissues, etc
- Formalin-Fixed Paraffin-Embedded

RT-PCR

- Positive
- Negative
- Formalin-Fixed Paraffin-Embedded

ALK IHC

- Positive
- Negative

FISH

- Positive
- Negative (Very rare)
- anaplastic carcinoma etc.

ALK inhibitor

IHC: Immunohistochemistry
FISH: Fluorescence in situ hybridization
RT-PCR: Reverse-Transcription-Polymerase Chain Reaction

Companion Diagnostics Test for Alectinib

- **IHC**

  HISTOFINE ALK iAEP® Kit (NICHIREI BIOSCIENCES INC.)

  A step with a linker reaction is inserted after the reaction with the primary antibody to enable binding with more HRP-labeled polymers.

  The difference between standard IHC versus high-sensitivity IHC.

- **FISH**

  Vysis® ALK Break Apart FISH Probe Kit (ABBOTT JAPAN CO., LTD.)

**Abbreviations**

IHC: Immunohistochemistry

FISH: Fluorescence in situ hybridization
Lung Cancer Treatment Guideline
Recommendation Grades of ALK inhibitor

- **1st line ALK-rearranged NSCLC (Good Performance status)**
  
  Cytotoxic Chemotherapy (A)
  Crizotinib (C1)

- **2nd line ALK-rearranged NSCLC (Good Performance status)**
  
  Crizotinib (A)
  Docetaxel (B)
  Pemetrexed (B)
  Erlotinib (C1)
  Doublet Therapy (C2)

A: Strongly recommended based on solid scientific rationale
B: Recommended based on scientific rationale
C1: Can be considered although scientific rationale is not sufficient
C2: No clear scientific rationale is available to recommend
D: Not to recommend based on scientific rationale indicating ineffectiveness or harmfulness
## Clinical Trials of Crizotinib

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Patients</th>
<th>Phase</th>
<th>Crizotinib Dosage</th>
<th>Treatment arm</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROFILE 1001</td>
<td>ALK Positive</td>
<td>Phase I</td>
<td>250 mg twice daily in 28-day cycle</td>
<td>- Crizotinib</td>
<td>149</td>
</tr>
<tr>
<td>PROFILE 1005</td>
<td>ALK Positive previously treated at least 1 regimen</td>
<td>Phase II</td>
<td>250 mg twice daily in 21-day cycle</td>
<td>- Crizotinib</td>
<td>136</td>
</tr>
<tr>
<td>PROFILE 1007</td>
<td>ALK Positive previously treated at least 1 platinum regimen</td>
<td>Randomized Phase III</td>
<td>250 mg twice daily in 21-day cycle</td>
<td>- Crizotinib - Pemetrexed or Docetaxel</td>
<td>347</td>
</tr>
<tr>
<td>PROFILE 1014</td>
<td>ALK Positive previously un-treated</td>
<td>Randomized Phase III</td>
<td>250 mg twice daily in 21-day cycle</td>
<td>- Crizotinib - Pemetrexed + Cisplatin or Carboplatin</td>
<td>334</td>
</tr>
</tbody>
</table>

2) ClinicalTrials.gov  
4) ClinicalTrials.gov
Compared with Traditional Chemotherapy, ALK Inhibitor have Shown Better Outcome (PROFILE1007)

**Median Progression Free Survival in 2nd line treatment**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib</td>
<td>7.7</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Shaw et al. NEJM 2013

Hazard ratio for progression or death in the crizotinib group, 0.49 (95% CI, 0.37–0.64)
P<0.001 (log-rank test)
Alectinib Phase I/II (AF-001JP)
Phase I part

Phase I

Phase Ia
- Fasting
  - 20mg twice daily n=1
  - 40mg twice daily n=1
  - 80mg twice daily n=1
  - 160mg twice daily n=3
  - 240mg twice daily n=3
  - 300mg twice daily n=6

Phase Ib
- Non-Fasting
  - 240mg twice daily n=3
  - 300mg twice daily n=6

Phase II

300 mg twice daily (n=46)
- Fasting

Efficacy analysis (n=46)
- Safety analysis (n=58)

- Patients - ALK rearranged stage IIIB, IV, or Recurrent NSCLC
- Primary Endpoint
  - Dose Limiting Toxicity, Maximum Tolerated Dose, Safety, Pharmacokinetics
- Secondary Endpoint
  - Tumor Response

Alectinib Phase I/II (AF-001JP)
Summary of Phase I part

- No grade 4 adverse events and no DLTs were observed up to the highest dose (300 mg twice a day). MTD was not determined.

- No adverse drug reaction related to treatment discontinuation or interruption more than 7 days was observed.

- Maximum drug concentration (Cmax) and Area under the curve (AUC) in the blood tend to increase in linear fashion in the range of 20 to 300 mg dosage.

- No difference in Pharmacokinetics and Safety under light fasting and non-fasting conditions at 300 mg repeated dose twice a day.

- 300 mg twice a day dosage was determined as recommended dose for further investigation in Japan.

Alectinib Phase I/II (AF-001JP)

Phase II part

- The purpose of Phase II is to confirm the effectiveness of Alectinib for recommended dose determined in Phase I part

Patients - ALK rearranged stage IIIB, IV, or Recurrent NSCLC

Primary Endpoint
- Response Rate

Secondary Endpoint
- Safety, Efficacy (Progression Free Survival, Overall Survival), Pharmacokinetics

Alectinib Phase I/II (AF-001JP)
Phase II Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Phase II (Efficacy Analysis) n=46, n (%)</th>
<th>300mg twice daily (Safety Analysis) n=58, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Years (range)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>48.0 (26-75)</td>
<td>49.5 (26-75)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male / Female</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22 (47.8) / 24 (52.2)</td>
<td>25 (43.1) / 33 (56.9)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>0 / 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 (43.5) / 26 (56.5)</td>
<td>24 (41.4) / 34 (58.6)</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Never</td>
<td></td>
</tr>
<tr>
<td></td>
<td>27 (58.7)</td>
<td>35 (60.3)</td>
</tr>
<tr>
<td></td>
<td>Present / Former</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (2.2) / 18 (39.1)</td>
<td>1 (1.7) / 22 (37.9)</td>
</tr>
<tr>
<td>Histological Findings</td>
<td>Adenocarcinoma / Squamous / Large</td>
<td></td>
</tr>
<tr>
<td></td>
<td>46 (100.0) / 0 / 0</td>
<td>58 (100.0) / 0 / 0</td>
</tr>
<tr>
<td>Clinical Stage</td>
<td>IIIB / IV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (4.3) / 31 (67.4)</td>
<td>2 (3.4) / 37 (63.8)</td>
</tr>
<tr>
<td></td>
<td>Recurrent</td>
<td>13 (28.3) / 19 (32.8)</td>
</tr>
<tr>
<td>ALK diagnosis</td>
<td>IHC and FISH Positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>39 (84.8)</td>
<td>49 (84.5)</td>
</tr>
<tr>
<td></td>
<td>RT-PCR Positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 (15.2)</td>
<td>9 (15.5)</td>
</tr>
<tr>
<td>EGFR status</td>
<td>Wild -type / Mutation / Unknown</td>
<td></td>
</tr>
<tr>
<td></td>
<td>41(89.1)/ 0 / 5(10.9)</td>
<td>52 (89.7) / 0 / 6 (10.3)</td>
</tr>
<tr>
<td>Previously</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy regimens</td>
<td>0 / 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (2.2) / 21 (45.7)</td>
<td>1 (1.7) / 21 (36.2)</td>
</tr>
<tr>
<td></td>
<td>2 / ≥3</td>
<td>9 (19.6) / 15 (32.6)</td>
</tr>
<tr>
<td></td>
<td>18 (31.0) / 18 (31.0)</td>
<td></td>
</tr>
<tr>
<td>Brain Meta</td>
<td>Yes / No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 (32.6) / 31 (67.4)</td>
<td>14 (30.4) / 32 (69.6)</td>
</tr>
<tr>
<td>Response Rate</td>
<td>Value</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>CR+PR</td>
<td>93.5% [95%CI: 82.1-98.6]</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>9 (19.6%)</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>34 (73.9%)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>1 (2.2%)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>NE</td>
<td>2 (4.3%)*</td>
<td></td>
</tr>
</tbody>
</table>

* Early Discontinuation

2014/1/31 Cut Off
Alectinib Phase I/II (AF-001JP)
Maximum Tumor Volume Change from Baseline

Maximum Response
CR  PR  SD  NE
(n=46)

2014/1/31 Cut off

*All lesions had disappeared, nodal diseases were normalized  RECIST1.1
Alectinib Phase I/II (AF-001JP)

Time to Tumor Volume Reduction Exceeding 30%

(n=46)

*1 cycle lasted 3 weeks.

2012/7/31 Cut Off

Alectinib Phase I/II (AF-001JP) Progression Free Survival

Median PFS: 27.7 months (95% CI: 26.9-NE)
1 year PFS rate: 83% (95% CI: 68-92)
2 years PFS rate: 76% (95% CI: 60-86)

Progression Free Survival Rate (%) vs. (Month)

No. at risk: 46, 43, 35, 34, 31, 14, 0, 0
2014/1/31 Cutoff

(n=46)
Alectinib Phase I/II (AF-001JP)
Safety

- Treatment-related adverse events reported in 20% or more. (n=58)

<table>
<thead>
<tr>
<th>Event</th>
<th>All Grade n(%)</th>
<th>Grade 1 n</th>
<th>Grade 2 n</th>
<th>Grade 3 n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Blood Bilirubin</td>
<td>21 (36.2)</td>
<td>5</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>20 (34.5)</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Increased AST</td>
<td>19 (32.8)</td>
<td>16</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Increased Blood Creatinine</td>
<td>18 (31.0)</td>
<td>10</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>17 (29.3)</td>
<td>14</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>17 (29.3)</td>
<td>15</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Decreased Neutrophil</td>
<td>15 (25.9)</td>
<td>1</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>15 (25.9)</td>
<td>12</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Increased Blood CPK</td>
<td>12 (20.7)</td>
<td>10</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Decreased WBC</td>
<td>12 (20.7)</td>
<td>3</td>
<td>8</td>
<td>1</td>
</tr>
</tbody>
</table>

Interstitial Lung Disease n=1 (1.7%): Grade 1

No AE over Grade 4
Chugai Internal Document
### Alectinib Phase I/II (AF-001JP)
#### Safety (Visual Disorder, Gastrointestinal Dysfunction)

(n=58)

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA ver. 13.1)</th>
<th>All Grade n(%)</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual Disorder*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred vision</td>
<td>1 (1.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>1 (1.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal Dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (15.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (8.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (1.7%)</td>
<td>0</td>
</tr>
</tbody>
</table>


Chugai Internal Document 38
Alectinib Phase I/II (AF-001JP)
Summary of Phase II part

● Alectinib was effective for ALK rearranged NSCLC
  Response Rate: 93.5% [95% CI: 82.1-98.6 ]^a)
● Estimated median PFS was 27.7 months [95% CI: 26.9-NE].^a)
● Median overall survival has not been reached, 2-year survival rate was 79% [95% IC: 63 - 89%].^b)
● Alectinib was generally well tolerated with manageable adverse event.
  – Grade 3 Adverse Event occurred in 16 patients (27.6%).

^a) 2014/1/31 Cut Off
^b) 2014/2/14 Cut Off
Alectinib vs Crizotinib
Randomized Phase III (J-ALEX Study)

Eligibility Criteria
- ALK Positive (IHC+FISH or RT-PCR)
- Stage IIIB/IV or Recurrent NSCLC
- At least 1 measurable region as defined by RECIST v1.1
- ECOG PS 0-2
- Chemo naïve or previously treated 1 Chemo regimen (ALKi naïve)

Primary endpoint
- PFS (RECIST v1.1)

Secondary endpoints
- OS
- ORR
- PRO/HRQoL
- CNS-PFS
- Safety
- Pharmacokinetics

Randomized

Alectinib 300 mg twice/day p.o. (n=100)

Crizotinib 250 mg twice/day p.o. (n=100)

1:1

n=200

Stratification factor:
ECOG PS (0/1 vs. 2), Treatment Line (1st vs. 2nd)
Clinical stage (ⅢB/Ⅳ vs. recurrent)
ALECENSA®
Postmarketing Safety Measures

Chiaki Iiyama
Pharmacovigilance Dept.
Chugai Pharmaceutical Co., Ltd.
1. Reasons for Implementing Safety Measures

2. Conditions for approval
   - Implement drug use surveillance for all patients
   - Implement appropriate distribution control

3. Conclusions
1. Reasons for Implementing Safety Measures

- **A very limited number of patients, who received approved clinical dose, participated in Japanese clinical studies.**
  - Only 58 patients received the clinical dose (300 mg, twice daily) during the Japanese Phase I / II clinical trial.

- **There is a possibility that serious adverse reactions (ADRs) may occur during actual clinical use.**
  - Distribution control must be implemented so that ALECENSA® will only be used in patients where this treatment is appropriate, under the care of physicians with the appropriate knowledge and experience with cancer chemotherapy, in a medical institution fully capable of dealing with medical emergencies.

**Strict safety measures are required for the appropriate use of ALECENSA®.**
1. Reasons for Implementing Safety Measures

Package insert: Warning section

WARNINGS

1. ALECENSA® should be administered at a medical institution fully capable of handling emergency situations, under the supervision of a physician who is knowledgeable and experienced in cancer chemotherapy, and only in patients for whom ALECENSA® therapy is judged to be appropriate. Before the start of treatment, the benefits and risks of ALECENSA® should be fully explained to patients or their families, and ALECENSA® should be administered only after informed consent has been obtained.

2. Interstitial lung disease may develop in patients given ALECENSA®. Patients should therefore be carefully monitored, such as by checking for incipient symptoms (e.g., shortness of breath, dyspnea, cough, and pyrexia) or performing chest CT. If there are any abnormalities, appropriate measures, such as discontinuing ALECENSA® treatment, should be taken. In the initial treatment phase, patients should also be hospitalized or supervised under equivalent conditions to carefully monitor for serious adverse reactions such as interstitial lung disease (see Careful Administration, Important Precautions, and Clinically significant adverse reactions).
1. Reasons for Implementing Safety Measures

Package insert: Contraindication section

CONTRAINDICATIONS (ALECENSA® is contraindicated in the following patients)

1. Patients with a history of hypersensitivity to any of the ingredients of ALECENSA®

2. Women who are or may be pregnant (see Use during Pregnancy, Delivery, or Lactation)
2. Conditions for Approval

The following Conditions for approval were attached in order to ensure the appropriate use of ALECENSA®. These included the implementation of drug use surveillance of all patients, and appropriate distribution control.

- **Implement drug use surveillance of all patients**
  A very limited number of patients participated in Japanese clinical studies. Therefore, drug use surveillance of all patients receiving ALECENSA® after launch should be conducted until data for a set number of patients have been accumulated. These data should be used to understand the background of patients using ALECENSA®, to collect early-phase safety and efficacy data on ALECENSA®, and to take any necessary measures for appropriate use of ALECENSA®.

- **Implement appropriate distribution control**
  The MAH should take measures necessary to ensure that ALECENSA® is administered only under the supervision of a physician, medical institution, and supervising pharmacist experienced with diagnosis of and chemotherapy for lung cancer and capable of adequately managing the risks, etc., of ALECENSA® treatment.
## Implement Drug Use Surveillance (All Patient Surveillance)

<table>
<thead>
<tr>
<th>Objective of the surveillance</th>
<th>To investigate the following aspects of drug use in actual clinical practice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Detection of unexpected adverse drug reactions.</td>
</tr>
<tr>
<td></td>
<td>2. To understand the incidence of adverse drug reactions including interstitial lung disease and liver function disorder.</td>
</tr>
<tr>
<td></td>
<td>3. To discover factors that may affect the onset of adverse drug reactions</td>
</tr>
<tr>
<td></td>
<td>4. Information regarding efficacy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Priority survey items</th>
<th>Interstitial lung disease, liver function disorder, and decreased neutrophil count/decreased white blood cell count</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Subject to surveillance</th>
<th>All patients administered ALECENSA® during the enrollment period</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Target number of patients</th>
<th>1,000 patients</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Scheduled enrollment period</th>
<th>For 18 months from ALECENSA® launch (Even after this enrollment period for the drug use surveillance is over, all patients need to be enrolled until PMDA agreed to release from the condition for approval regarding the all patient surveillance.)</th>
</tr>
</thead>
</table>
Implement Appropriate Distribution Control

**Confirmation of institution and physician requirements for drug use**

**Institution requirements**

1) Staffed by physicians who satisfy the physician requirements for use
2) **Able to receive patient calls 24 hours a day**, with the ability to deal and provide emergency care including in-patient treatment either at their own facility or an affiliated institution.
3) Able to perform chest CT examinations at own facility or an affiliated medical institution.
4) **Able to provide appropriate treatment for interstitial lung disease occur during this treatment** with ALECENSA®.
5) Able to cooperate with the Chugai safety measures for ALECENSA®.

**Physician requirements**

1) **Possesses adequate experience in lung cancer chemotherapy**, and is affiliated with relevant lung cancer-related medical societies such as the Japanese Society of Medical Oncology, The Japan Lung Cancer Society, or The Japanese Respiratory Society.
2) Will accommodate routine visits from Chugai medical representatives.
3) Will cooperate with the Chugai safety measures for ALECENSA®, including the careful selection of patients, etc.
Implement Appropriate Distribution Control

Provision of information to promote appropriate use

For Healthcare Professionals

For Patients

Appropriate Use Guide

ALECENSA® Handbook

Safety information on ALECENSA® is provided on our corporate website (for healthcare Professionals).
Implement Appropriate Distribution Control

Use of the ALECENSA® Emergency Contact Card

ALECENSA® Emergency Contact Card

[Front: Initial symptoms of clinically significant adverse reactions including ILD1)]

- Shortness of breath, difficulty breathing, persistent coughing, or fever
- Fever, yellowing of the whites of the eyes or skin, brownish urine, nausea, vomiting, abdominal bloating, loss of appetite, feeling listless
- Chills and fever
- Sudden severe stomach pain
- Chest pains, feeling of tightness, leg swelling and pain, shortness of breath, difficulty breathing

[Back: Emergency contact details]

- Emergency Contact Information
  - Medical Institution:
  - Hospital phone number:
  - Clinical Department:
  - Attending physician:
  - Patient Registration Card No.:

- Name:
- Phone Number:

Business Card size (57mm x 88mm)

1) ILD: Interstitial Lung Disease
Implement Appropriate Distribution Control

Careful selection of patients to be treated

All patients who will use the drug must be enrolled before drug administration and will be confirmed their eligibility for the drug. Conduct thorough promotion of proper use to ensure the drug is used appropriately.

All patients who will use the drug must be enrolled before drug administration

Confirm patient eligibility

Promote proper use by informing the prescribing physician about the package insert contents, if necessary.

Drug use surveillance (all-patient surveillance)
3. Conclusions

1. Reasons for implementing safety measures
2. Conditions for approval
   - Implement drug use surveillance in all patients
   - Implement appropriate distribution control
     - Confirm that institutions and prescribing physician fulfill all requirements
     - Provide information to promote appropriate use
     - Use of Emergency contact cards
     - Careful selection of patients to be treated

All new drugs and biosimilars receiving marketing authorization after April 1, 2013 must develop a risk management plan. Because of this, ALECENSA® Risk management plan was developed and described identified important safety specification, plans to conduct surveys and collect information on each safety specification, all of the measures taken to deal with each specifications including how to distribute the information. The risk management plan for ALECENSA® will soon be made available on the PMDA Website. http://www.info.pmda.go.jp
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