Aiming to become a "top pharmaceutical company"

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.

ALECENSA®

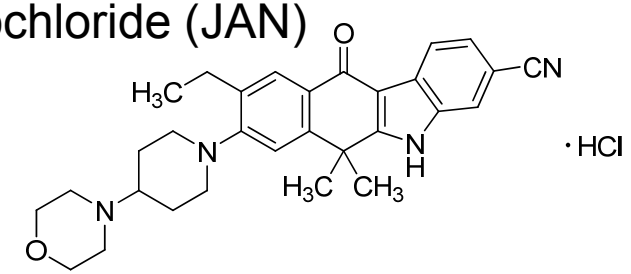
Outline of ALECENSA®

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)



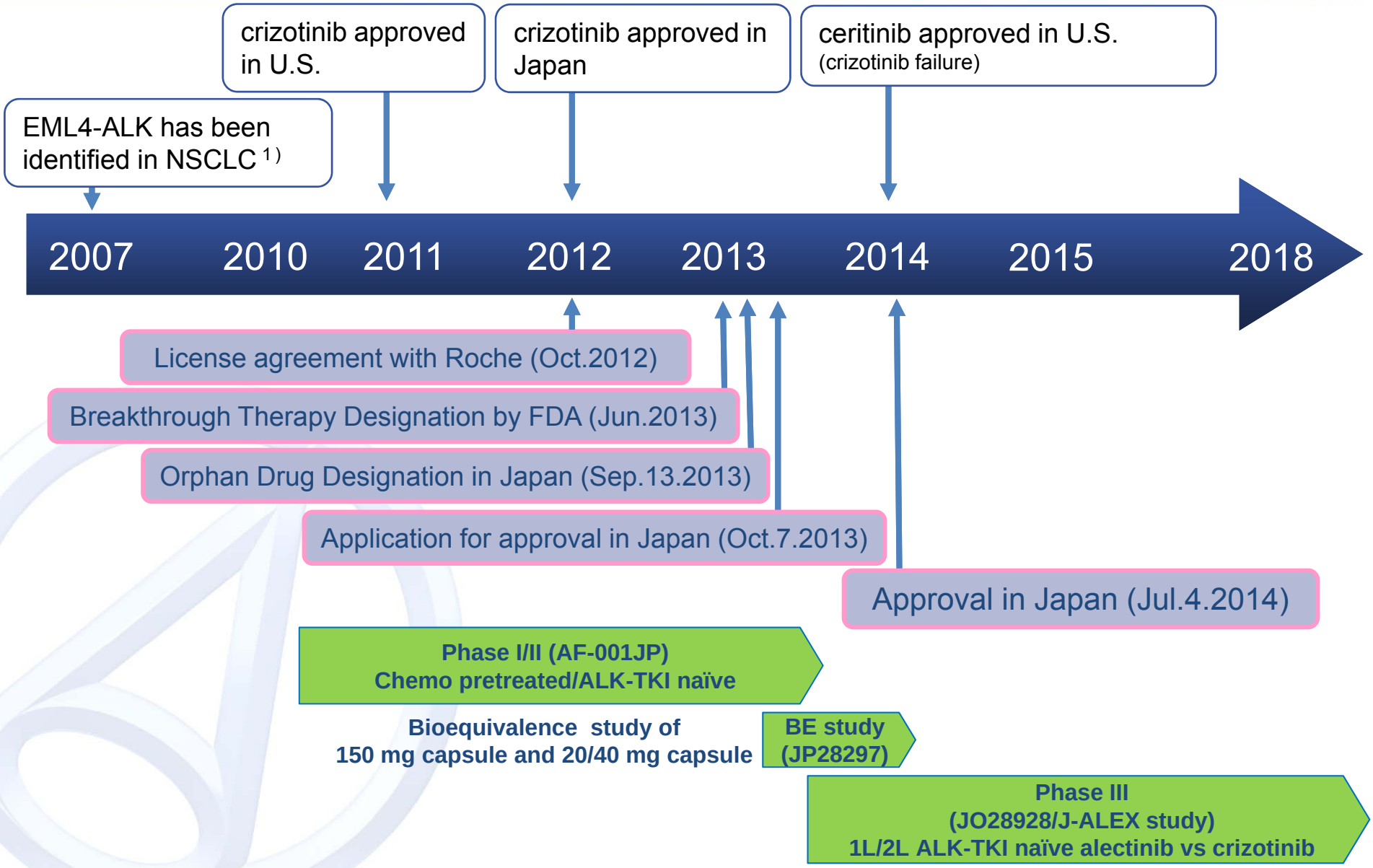
Molecular weight: 519.08

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)



1) Soda M, et al. Nature 2007; 448(7153): 561-6

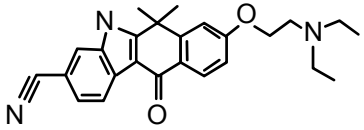
ALK Inhibitor Screening and Derivatization to ALECENSA®

① Compound library

High-throughput kinase inhibitor screening

Hit A | Hit B | Hit C | …

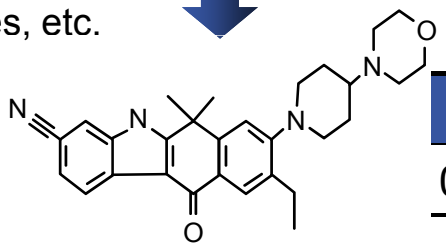
KARPAS-299 (NPM-ALK) mouse xenograft model (po, qd x11)



Lead compound

ED_{50}	MTD/ED_{50}
17 mg/kg	2.9-fold

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



CH5424802

ED_{50}	MTD/ED_{50}
0.81 mg/kg	>75-fold

ED50; effective dose causing 50% inhibition
MTD; maximum tolerated dose

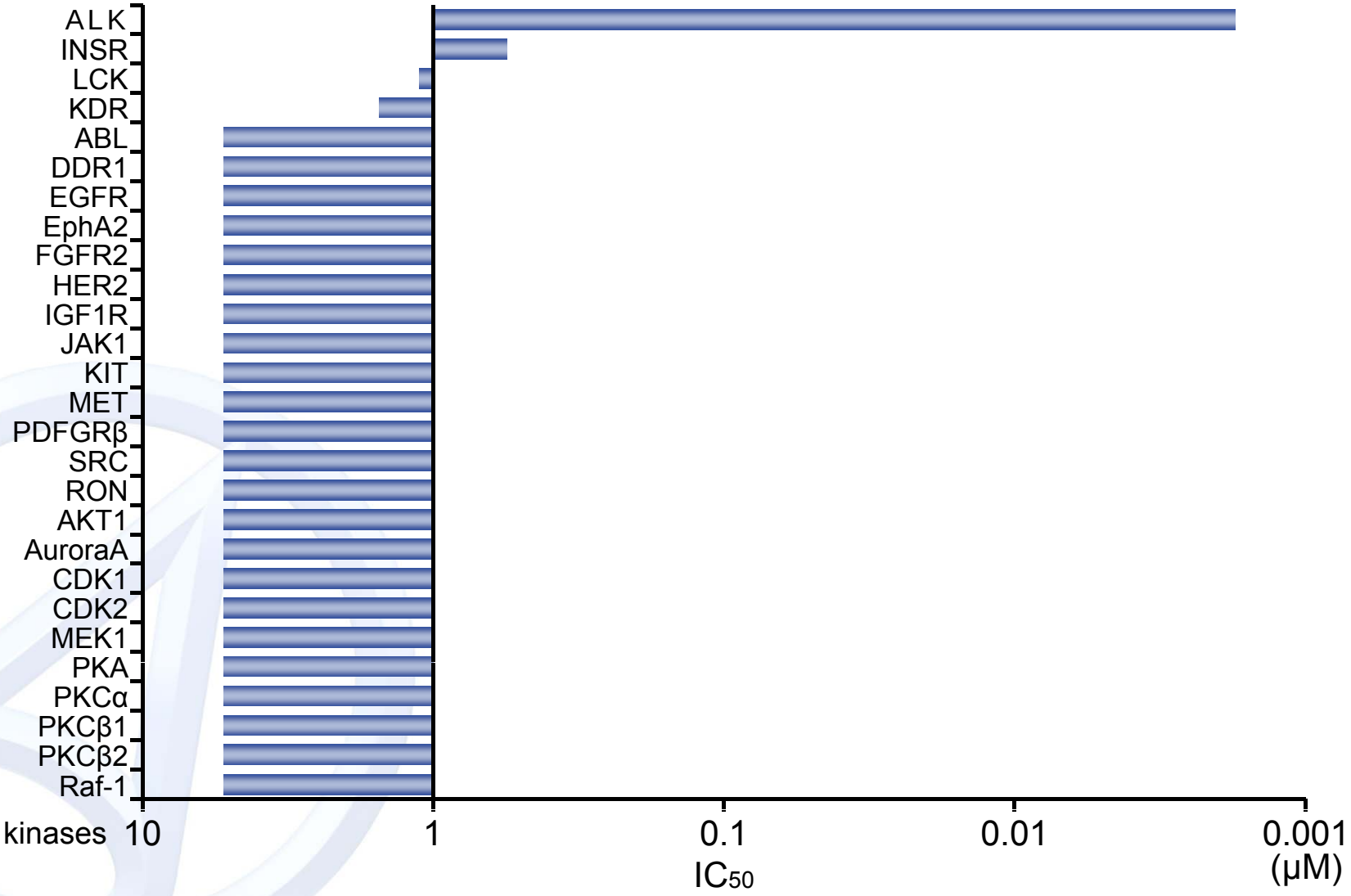
② Ultra high-throughput screening with a library of more than one million compounds

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

Synthesize almost 600 derivatives

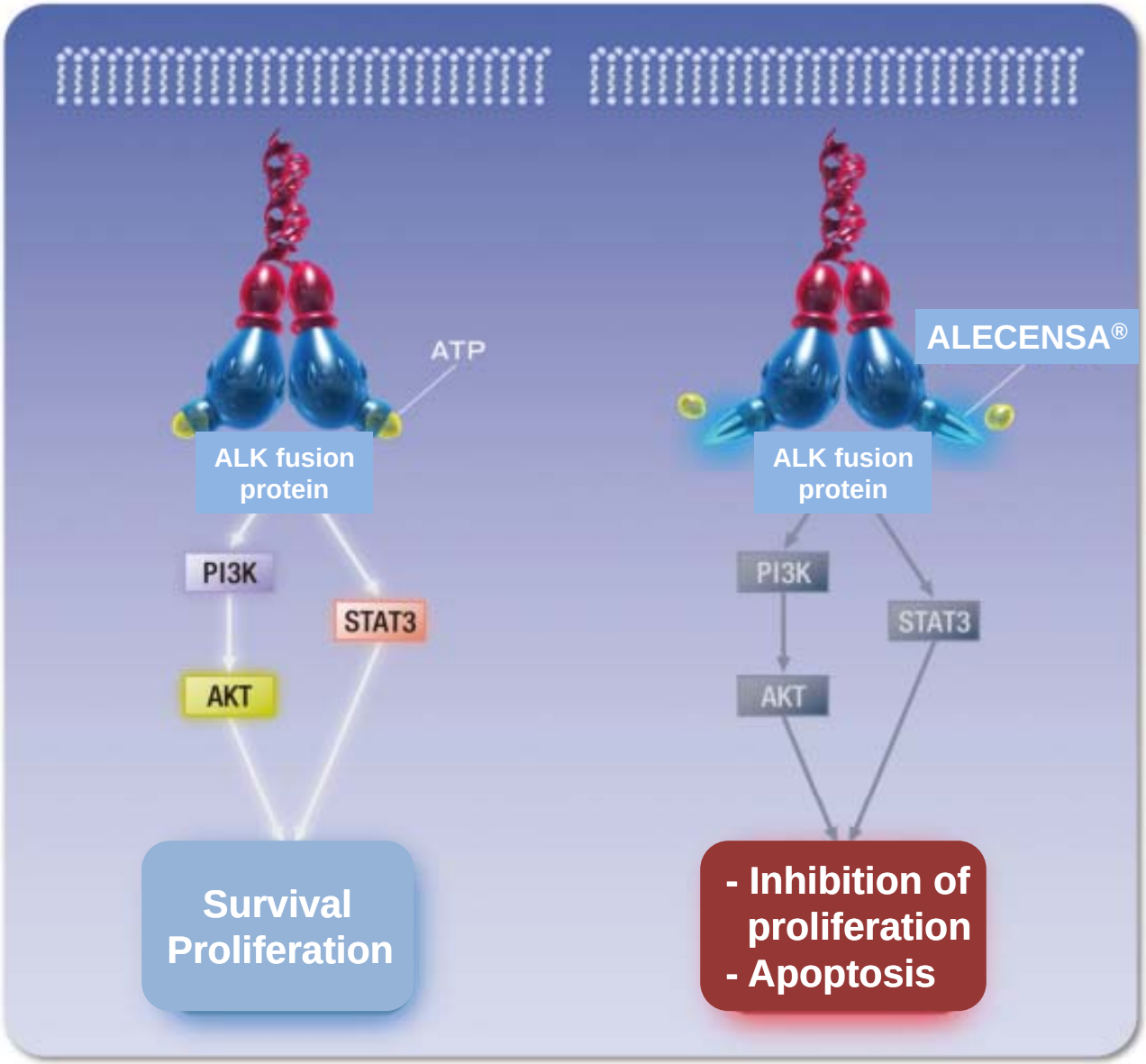
ALECENSA®

Kinase Inhibitory Profile of ALECENSA® (in vitro)



Modified from Sakamoto H, et al. Cancer Cell 2011;19(5):679-90

The Mechanism of Antitumor Activity of ALECENSA®



Conceptual Illustration

Modified from Sasaki T, et al. Clin Cancer Res 2011;17(23): 7213-8.

Description

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

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.)

抗悪性腫瘍剤/ALK阻害剤
劇薬、処方箋医薬品注)
薬価基準未収載
発売準備中
アレセンサ® カプセル20mg カプセル40mg
ALECENSA®
アレクチニブ塩酸塩カプセル
注)注意－医師等の処方箋により使用すること

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

1 Japan originated ALK inhibitor

ALECENSA® suppresses proliferation of ALK fusion gene-positive tumor cells by inhibiting ALK tyrosine kinase activity.

2 Efficacy in non-clinical studies

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.

3 Efficacy in Japanese Phase I/II study (AF-001JP)

In the Phase II part of AF-001JP study,

- The response rate was 93.5% (95% CI, 82.1-98.6). CR was19.6%
- Median PFS was 27.7 months (95% CI: 26.9-not estimable)
- 2-year survival rate was 79% (95% CI: 63-89)

4 Safety in Japanese Phase I/II study (AF-001JP)

In the case which patients were treated with 300 mg twice daily in AF-001JP study.

- Treatment-related adverse events were observed in 56 patients (96.6%).
- The most common treatment-related adverse events included increased blood bilirubin, dysgeusia and rash, increased AST (GOT) , and increased blood creatinine
- Clinically significant treatment-related adverse events included Interstitial lung disease, hepatic function disorder, decreased neutrophils, decreased white blood cells, gastrointestinal perforation, thromboembolism

modified from Product monograph

Reference:
Ongoing Global Clinical Studies

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

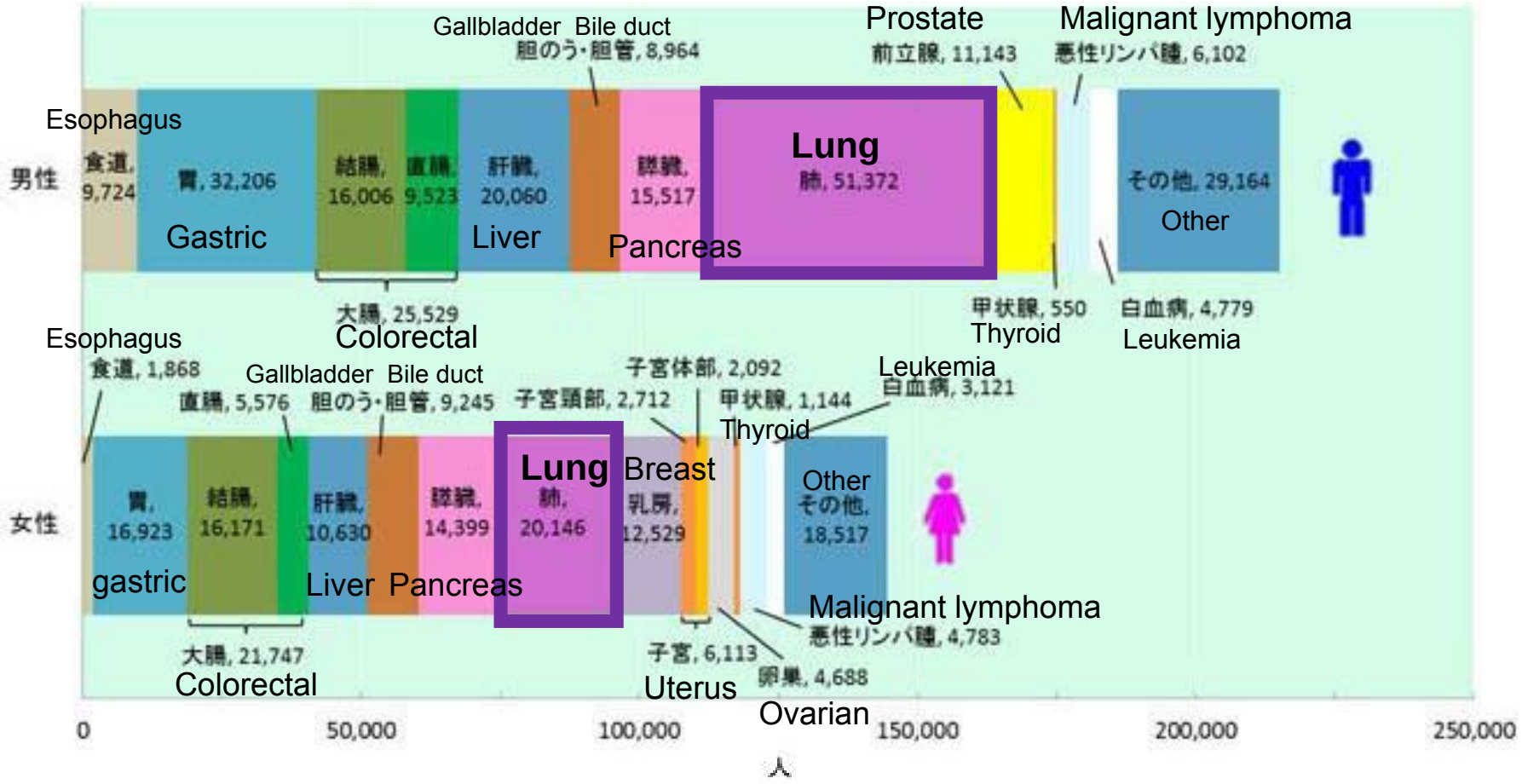
1) S.Gadgeel,et al.WCLC2013,O16.06 2) ClinicalTrials.gov

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

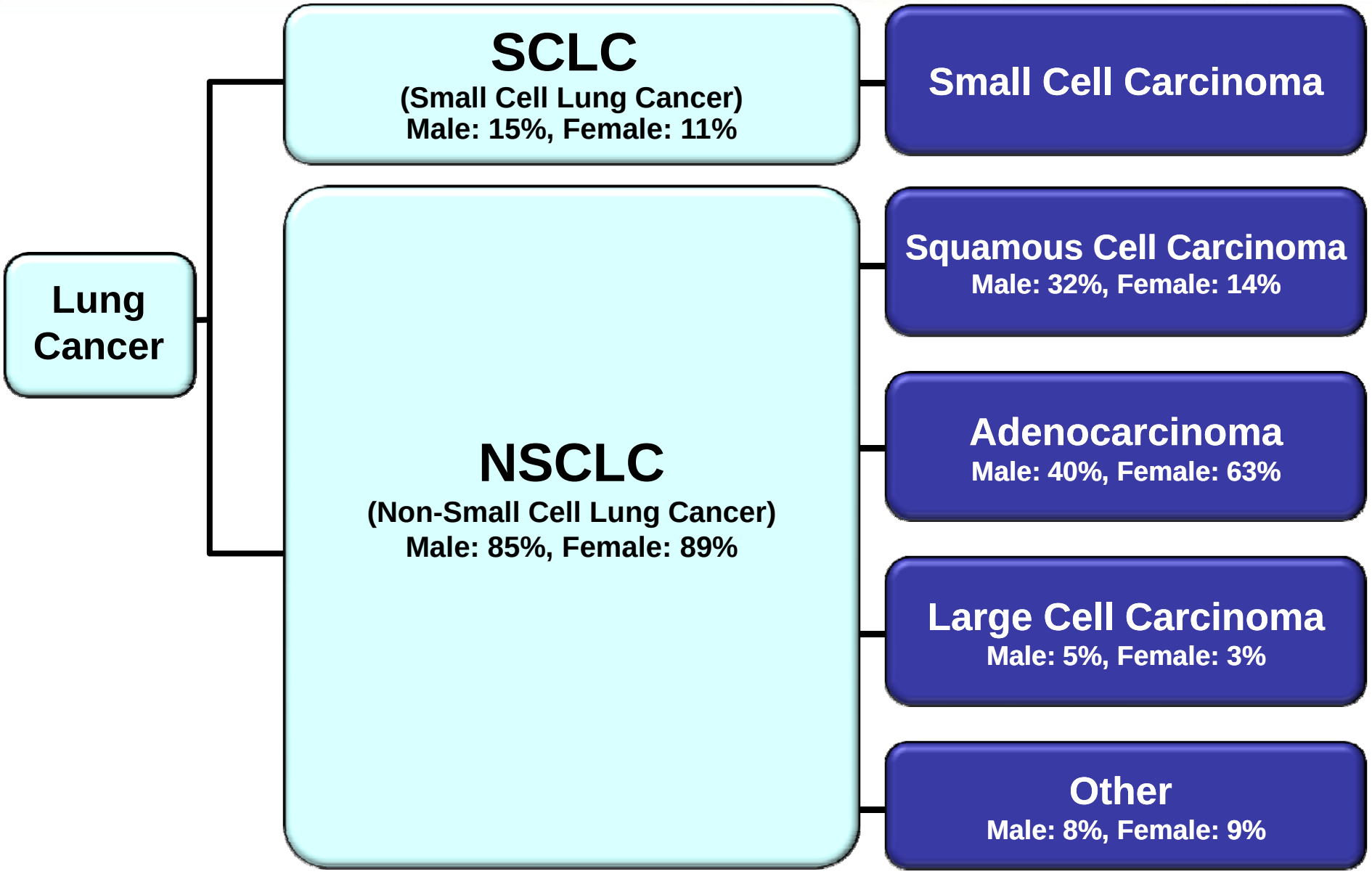
Death from Lung Cancer in Japan (2012)

- Male 51,372 Female 20,146



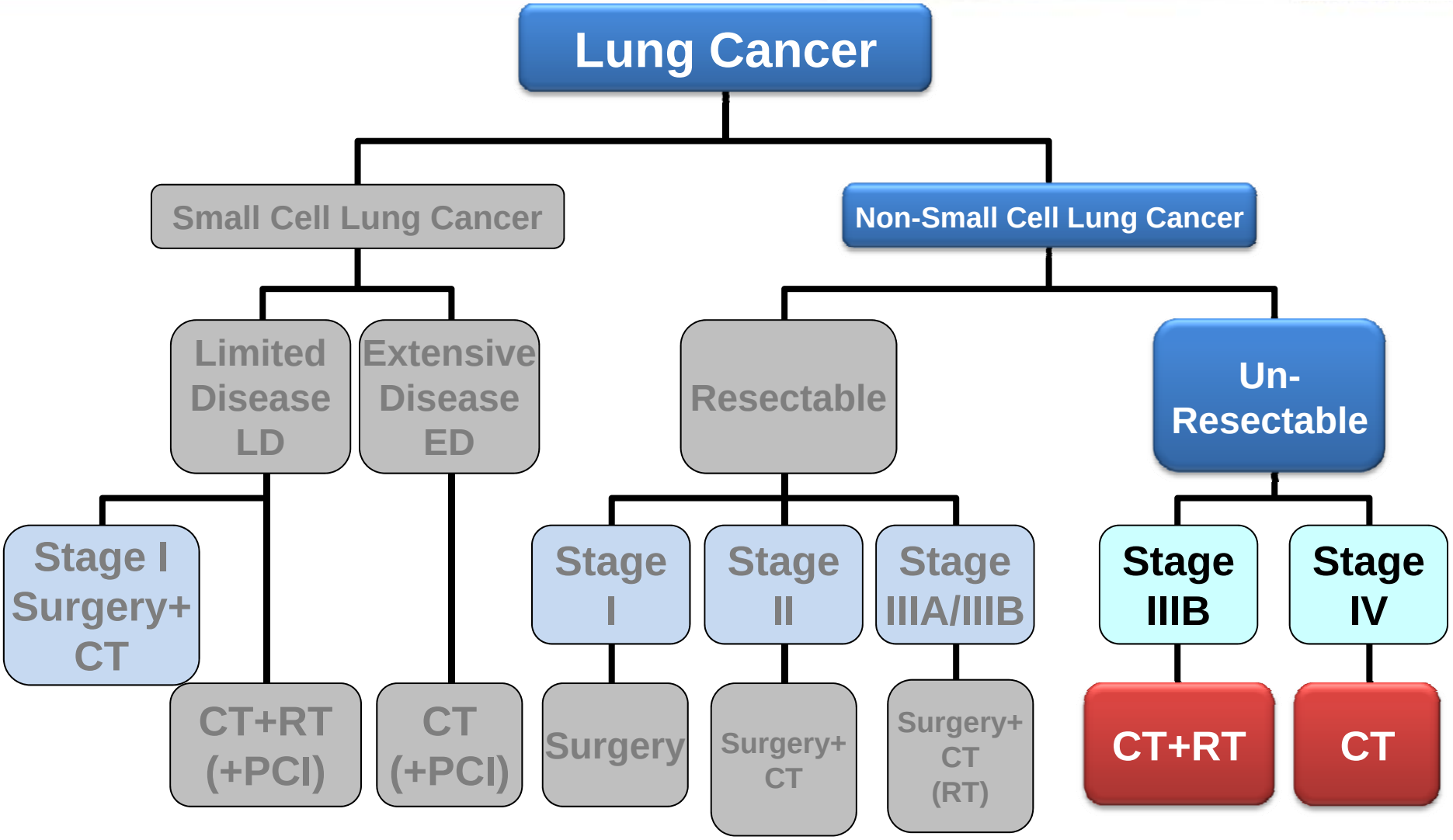
National Cancer Research Center. (URL; ganjyoho.jp)

Histological Classification of Lung Cancer



Cancer Incidence in Five Continents, vol.IX, ed by Curado MP et al. IARC Scientific Publications, No.160, IARC, Lyon, 2007

Treatment Algorithm of Lung Cancer

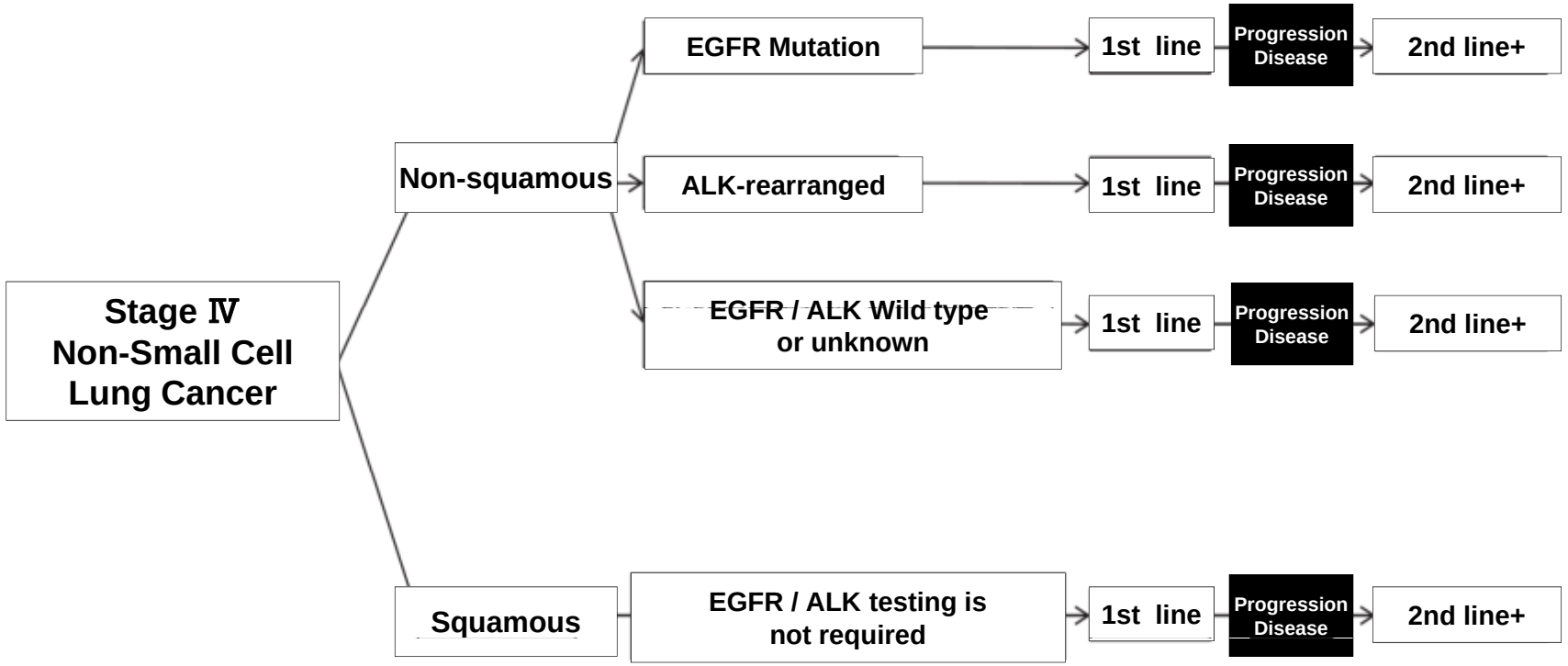


CT: Chemo Therapy **RT:** Radio Therapy **PCI:** Prophylactic cranial irradiation

Rinsho Shyuyou Gaku, 3rd ed. Tokyo; Gan To Kagaku Ryoho Co. Ltd.

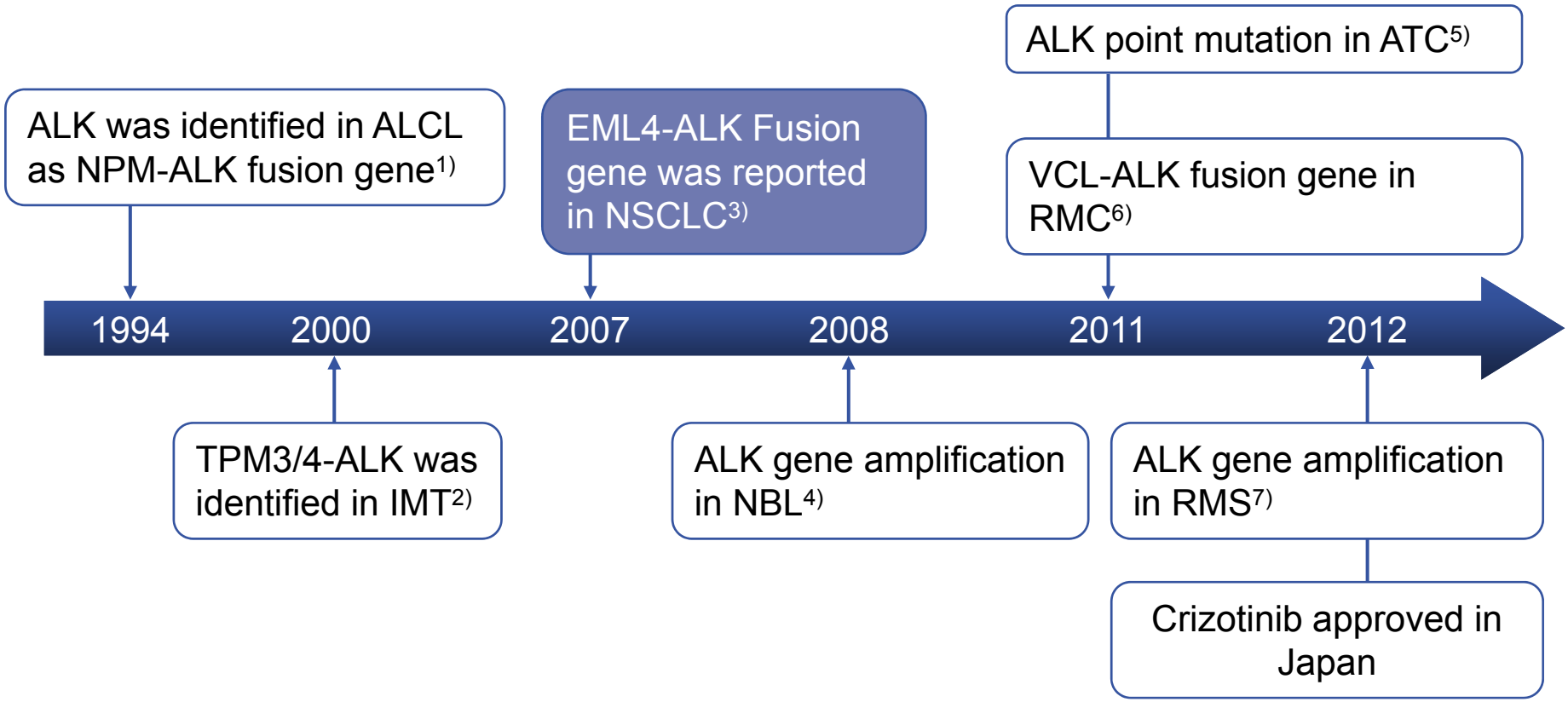
Lung Cancer Treatment Guideline (2014)

Treatment of Stage Ⅳ Non-Small Cell Lung Cancer



http://www.haigan.gr.jp/modules/guideline/index.php?content_id=3

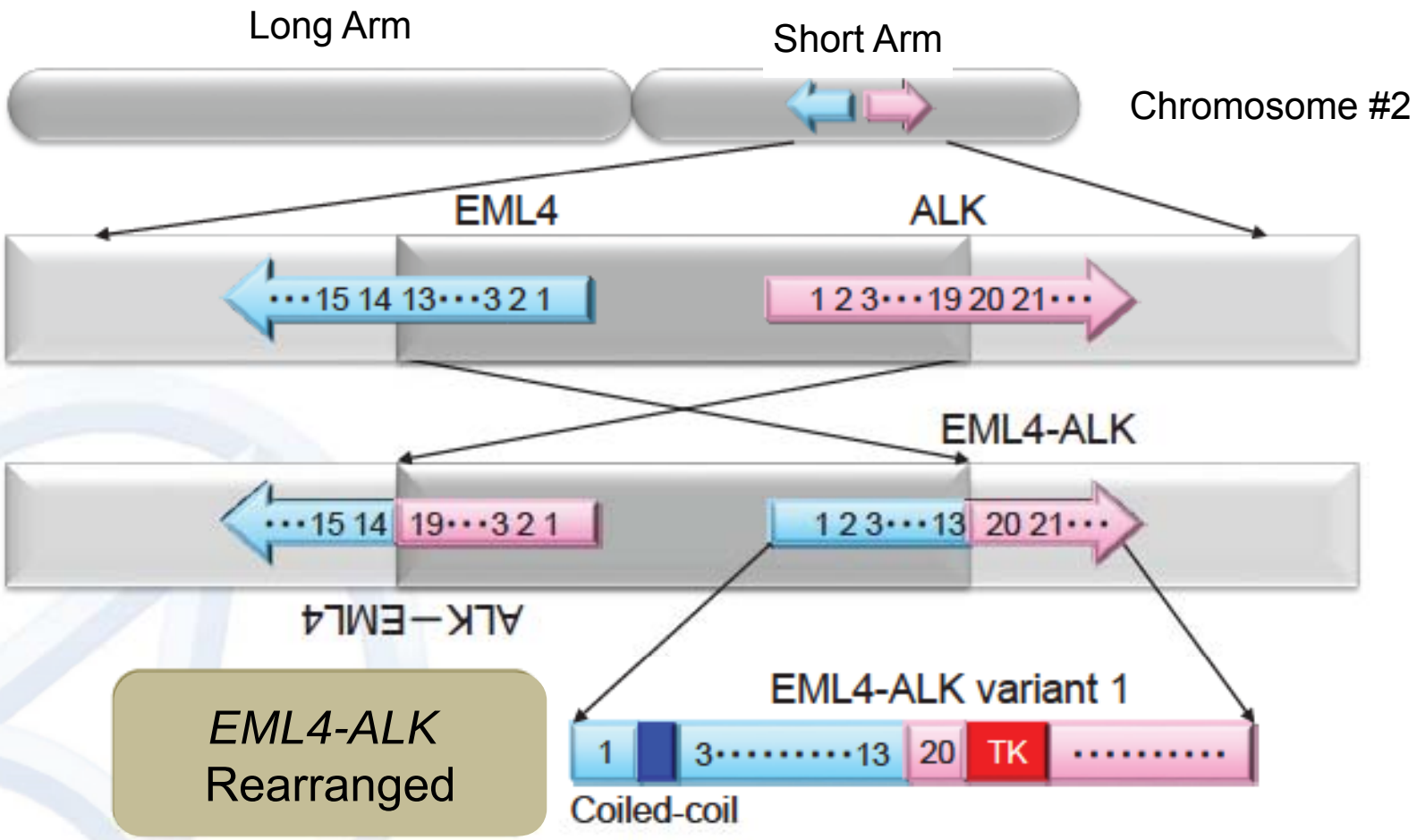
History of the Research of the ALK Gene in Various Cancer



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

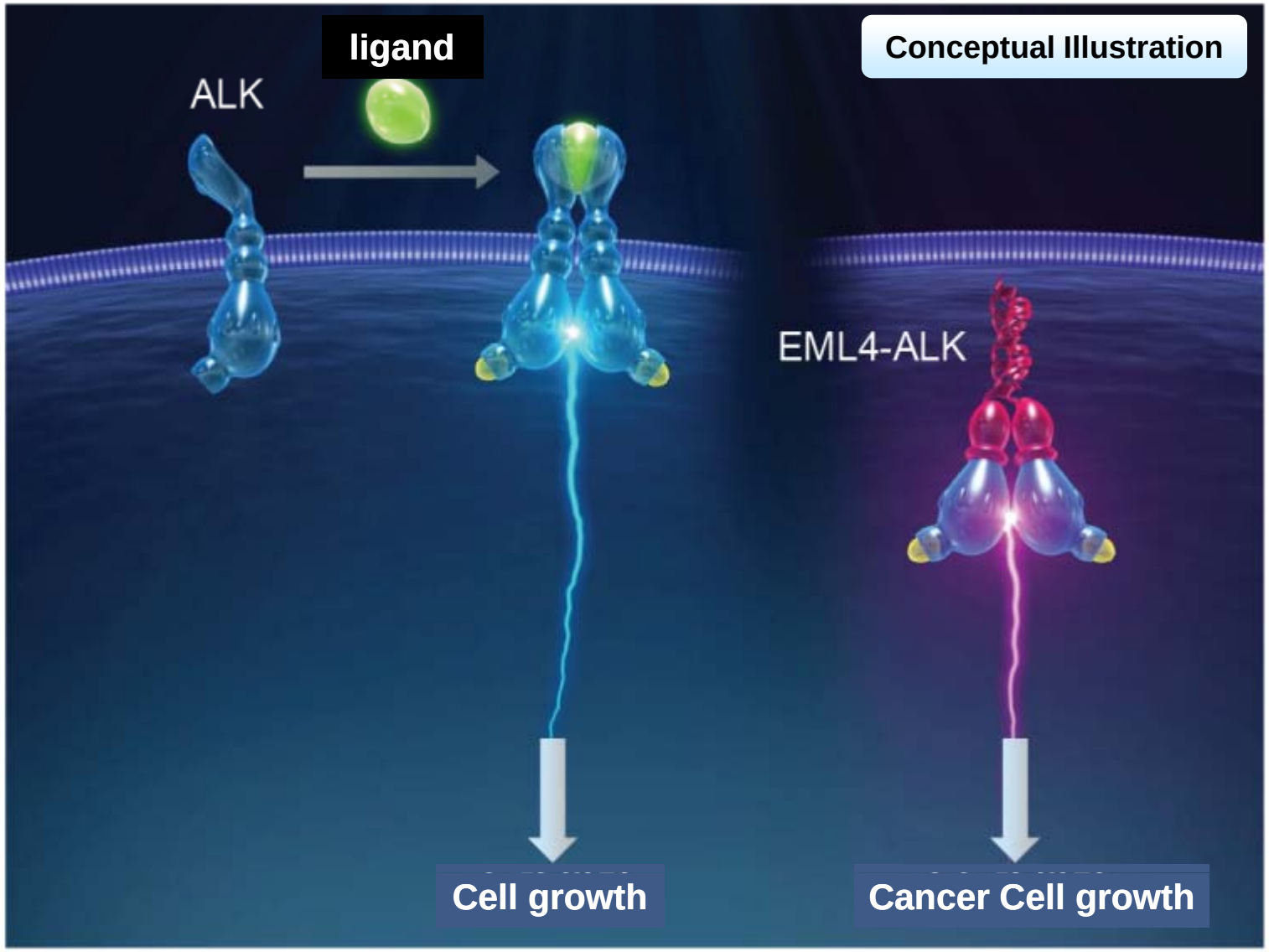
1) Morris SW, et al. Science 1994; 263(5151): 1281-4
2) Lawrence B, et al. Am J Pathol 2000; 157(2): 377-84
3)Soda M, et al. Nature 2007; 448(7153): 561-6
4) Carén H, et al. Biochem J 2008; 416(2): 153-9
5) Murugan AK, et al. Cancer Res 2011; 71(13): 4403-11
6) Mariño-Enríquez A, et al. Genes Chromosomes Cancer 2011; 50(3): 146-53
7) van Gaal JC, et al. J Clin Oncol 2012, 30(3): 308-15

EML4-ALK Rearranged



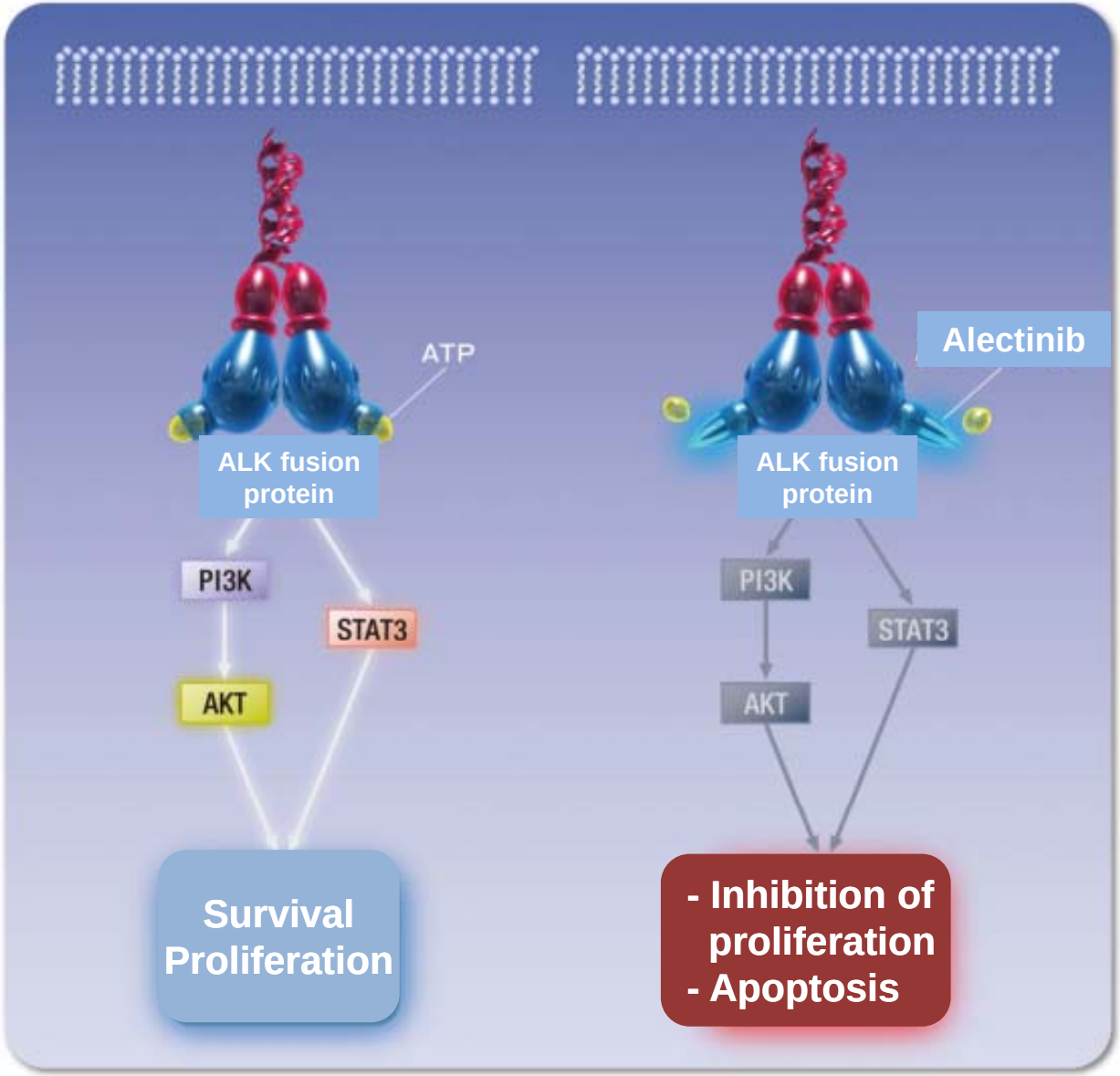
Guidance for ALK Gene Testing in Lung Cancer Patients ver 1.2, Japan Lung Cancer Society .

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



Modified from Mano H. Cancer Sci 2008;99(12): 2349-2355.

Mechanism of Alectinib



Conceptual Illustration

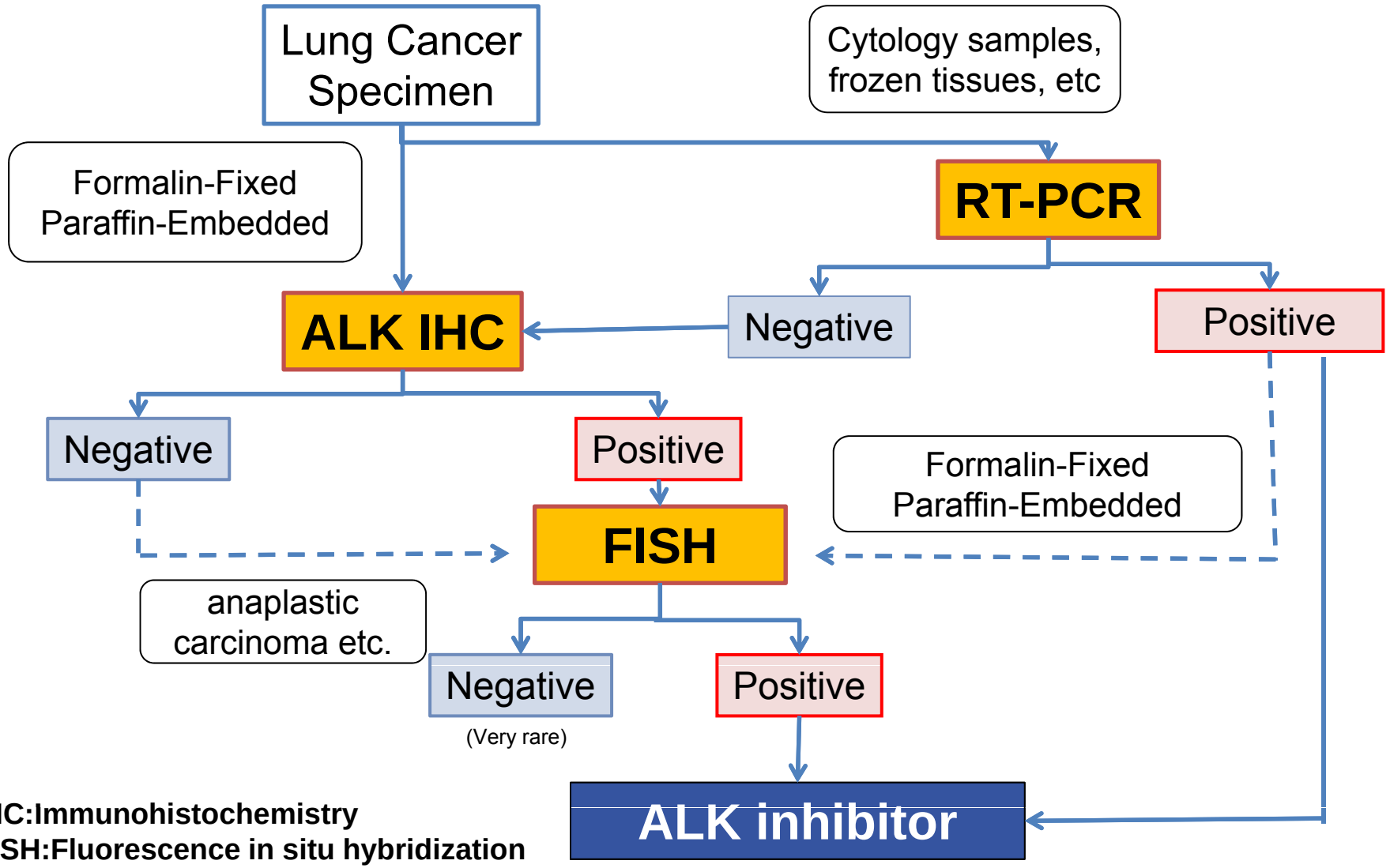
Modified from Sasaki T, et al. Clin Cancer Res 2011;17(23): 7213-8.

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



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

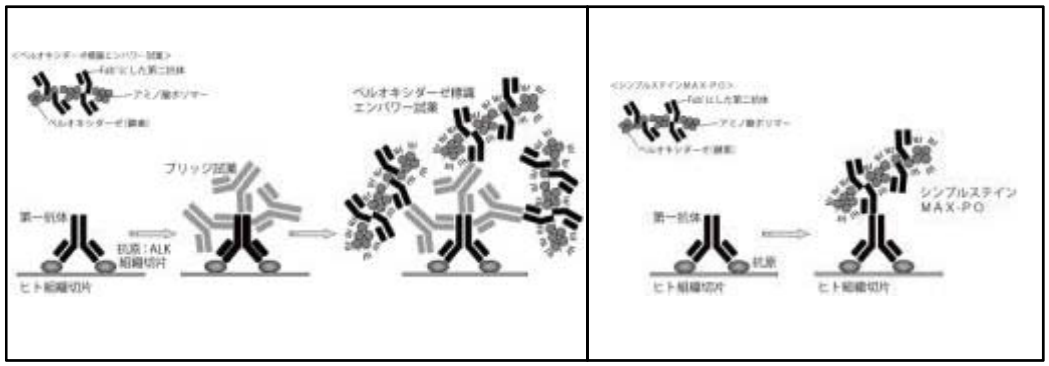
Modified from Guidance for ALK Gene Testing in Lung Cancer Patients ver 1.2, Japan Lung Cancer Society .

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.)

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

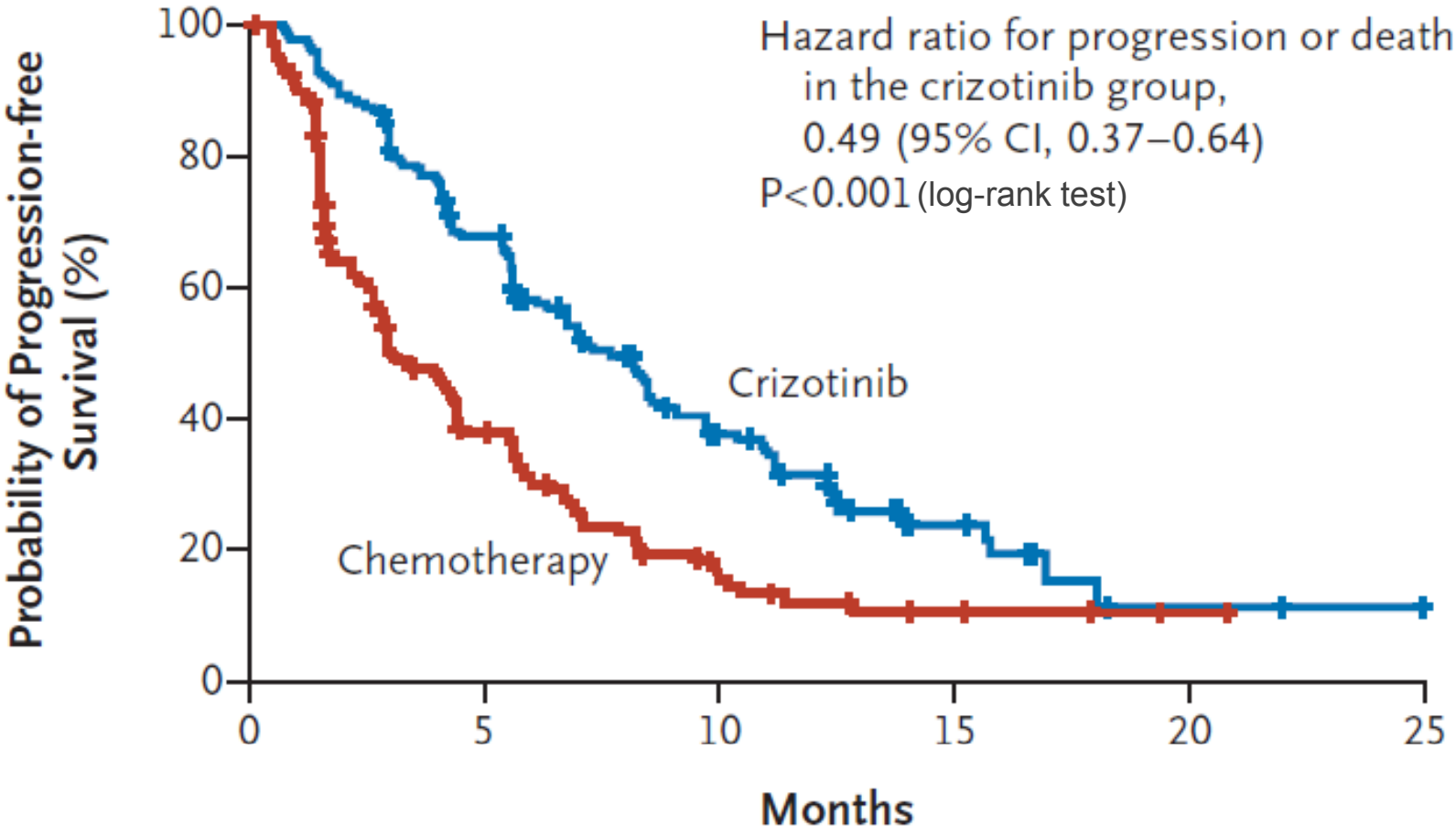
Study Name	Patients	Phase	Crizotinib Dosage	Treatment arm	N
PROFILE 1001 [1)]	ALK Positive	Phase I	250 mg twice daily in 28-day cycle	- Crizotinib	149
PROFILE 1005 [2)]	ALK Positive previously treated at least 1 regimen	Phase II	250 mg twice daily in 21-day cycle	- Crizotinib	136
PROFILE 1007 [3)]	ALK Positive previously treated at least 1 platinum regimen	Randomized Phase III	250 mg twice daily in 21-day cycle	- Crizotinib - Pemetrexed or Docetaxel	347
PROFILE 1014 [4)]	ALK Positive previously un-treated	Randomized Phase III	250 mg twice daily in 21-day cycle	- Crizotinib - Pemetrexed + Cisplatin or Carboplatin	334

1)Camidge DR, et al. Lancet Oncol 2012; 13(10): 1011-9 2)ClinicalTrials.gov
3)Shaw AT, et al. N Engl J Med 2013, 368(25): 2385-94 4)ClinicalTrials.gov

Compared with Traditional Chemotherapy, ALK Inhibitor have Shown Better Outcome (PROFILE1007)

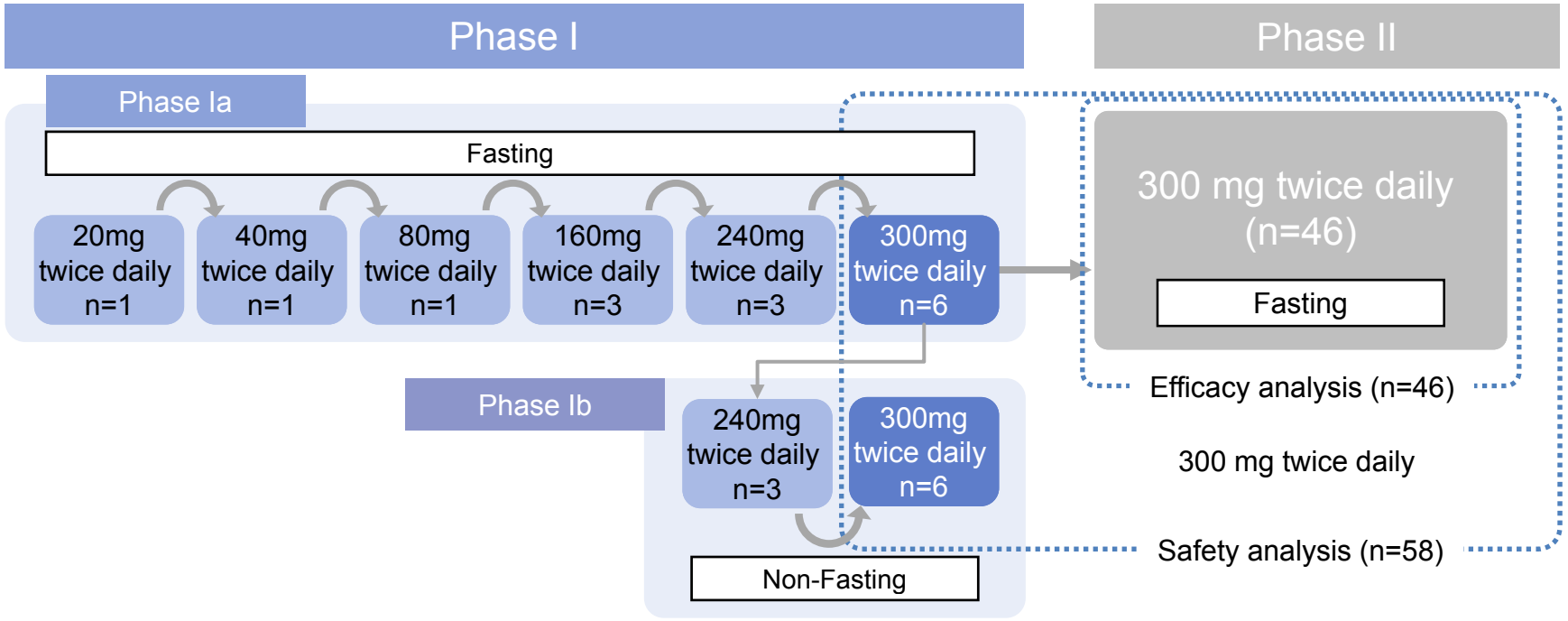
Median Progression Free Survival in 2nd line treatment

Crizotinib	7.7 months
Chemotherapy	3.0 months



Shaw et al. NEJM 2013

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



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

- Primary Endpoint
  - Dose Limiting Toxicity, Maximum Tolerated Dose, Safety, Pharmacokinetics
- Secondary Endpoint
  - Tumor Response

Seto T, et al. Lancet Oncol 2013;14(7): 590-8

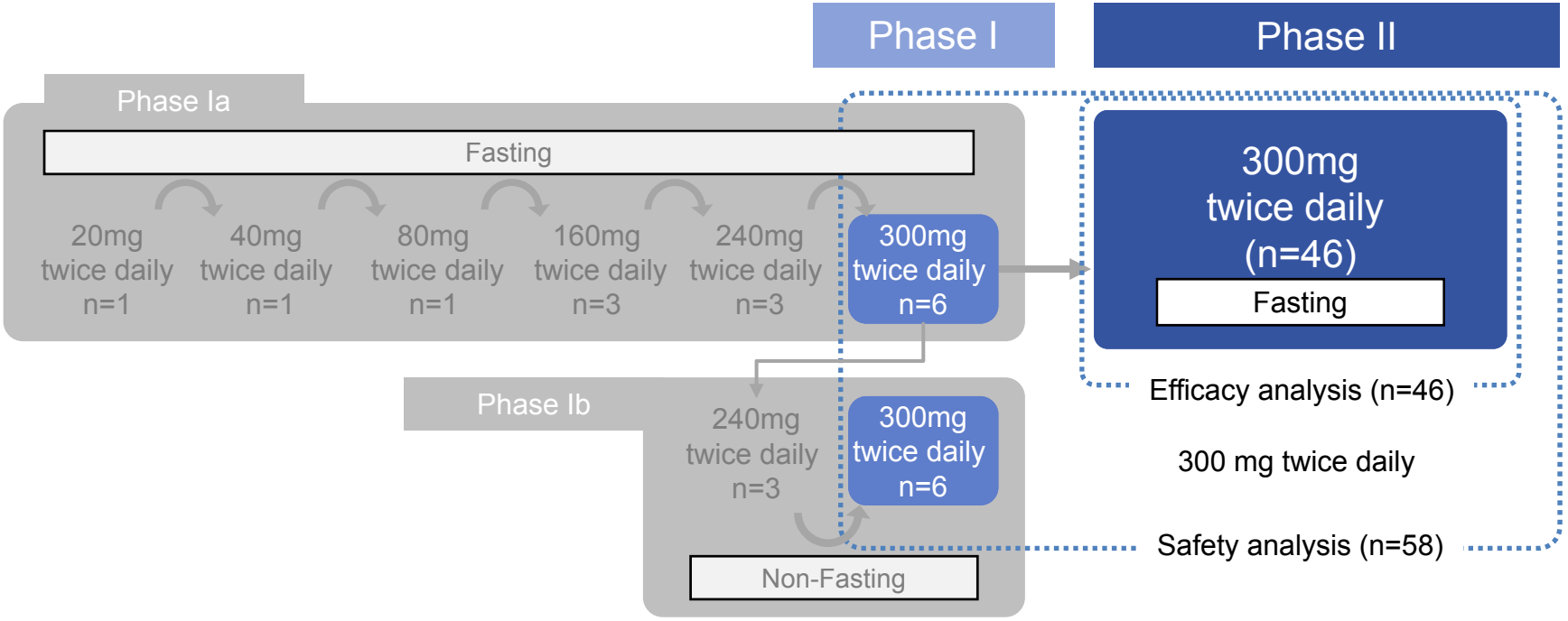
Alectinib Phase I/II (AF-001JP)
Summary of Phase I part

- 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.

Seto T, et al. Lancet Oncol 2013;14(7): 590-8

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

Seto T, et al. Lancet Oncol 2013;14(7): 590-8

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

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

Alectinib Phase I/II (AF-001JP)
Response Rate

(n=46)

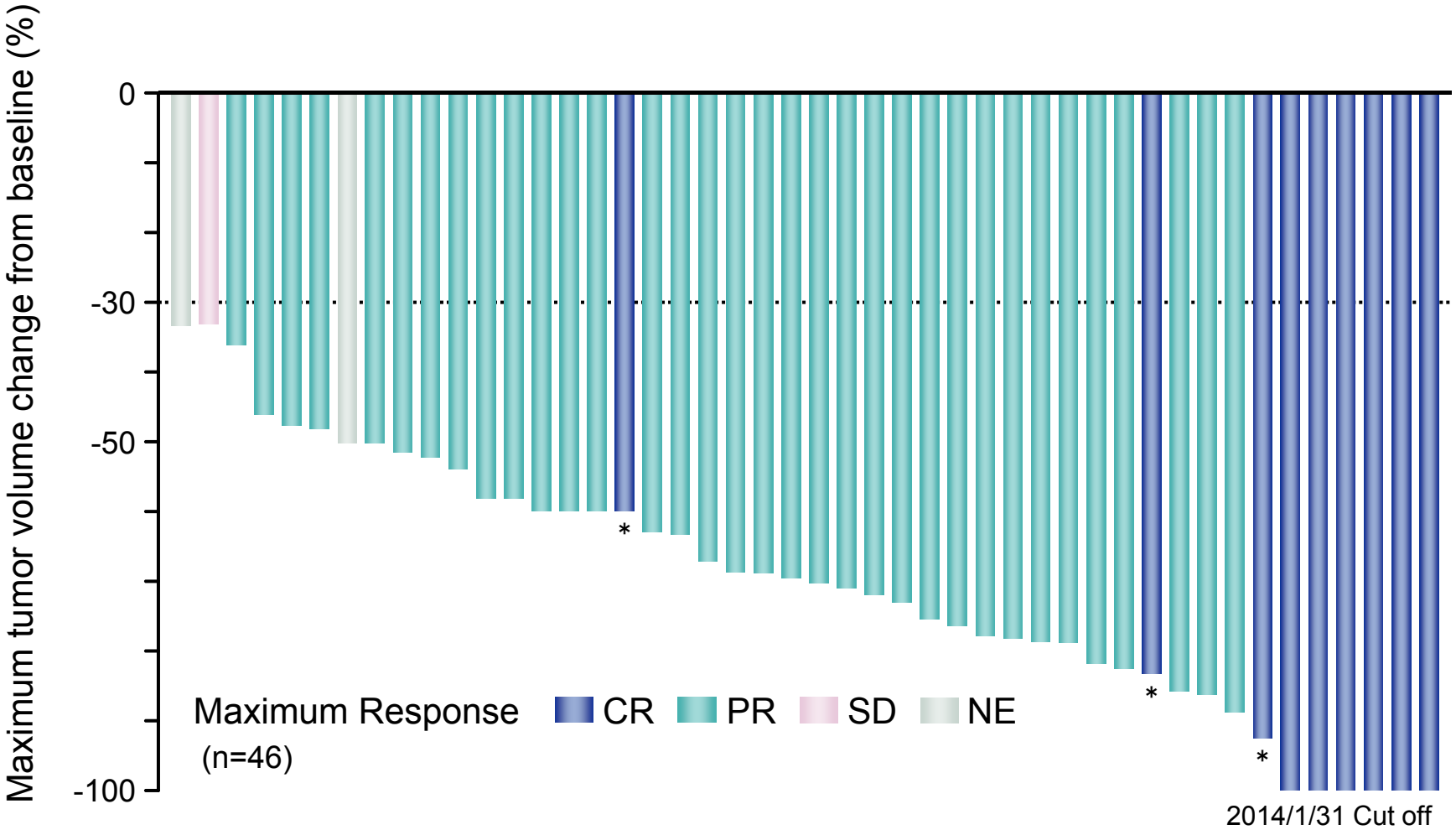
Response Rate	
CR+PR	93.5% [95%CI: 82.1-98.6]
CR	9 (19.6%)
PR	34 (73.9%)
SD	1 (2.2%)
PD	0 (0%)
NE	2 (4.3%)*

* Early Discontinuation

2014/1/31 Cut Off

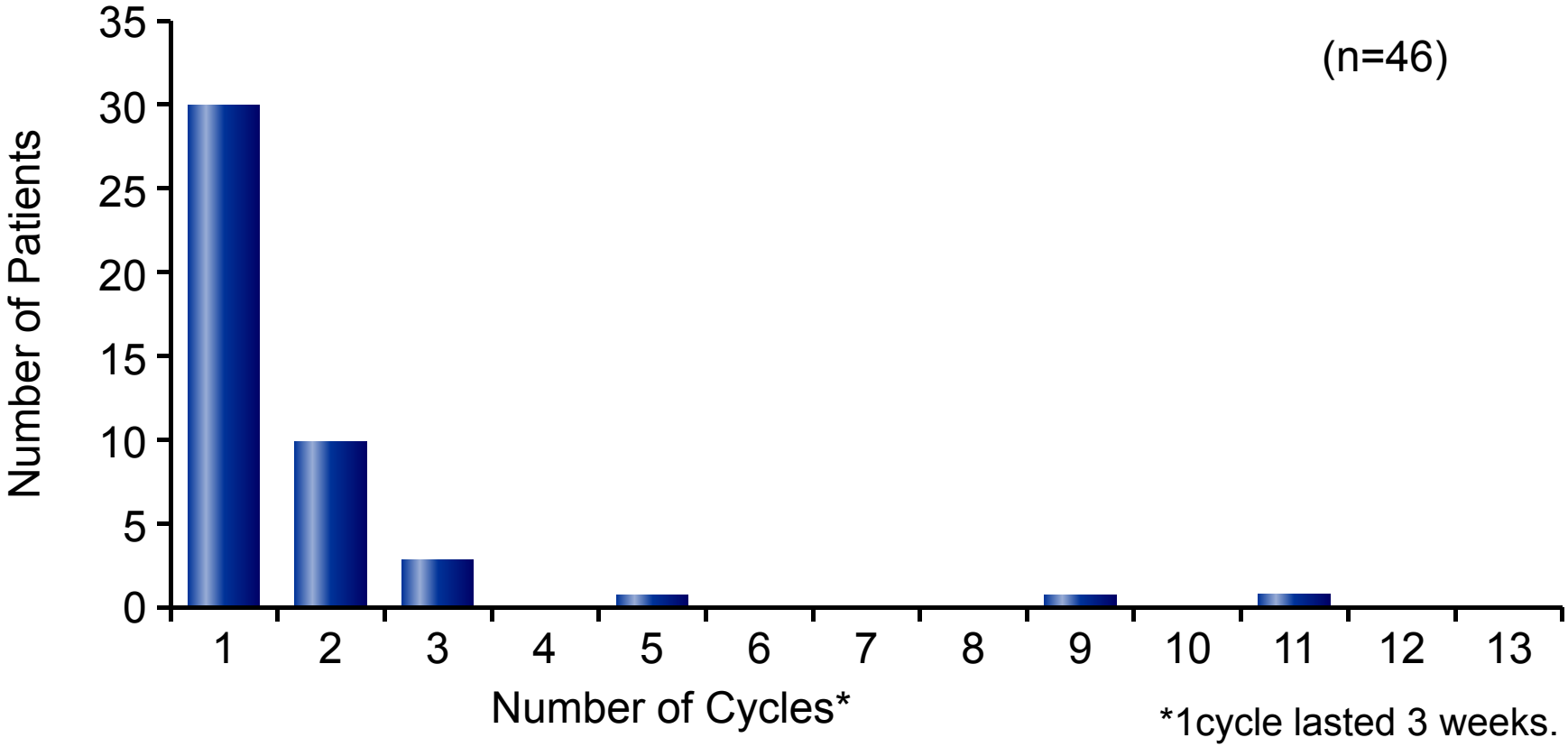
Alectinib Phase I/II (AF-001JP)

Maximum Tumor Volume Change from Baseline



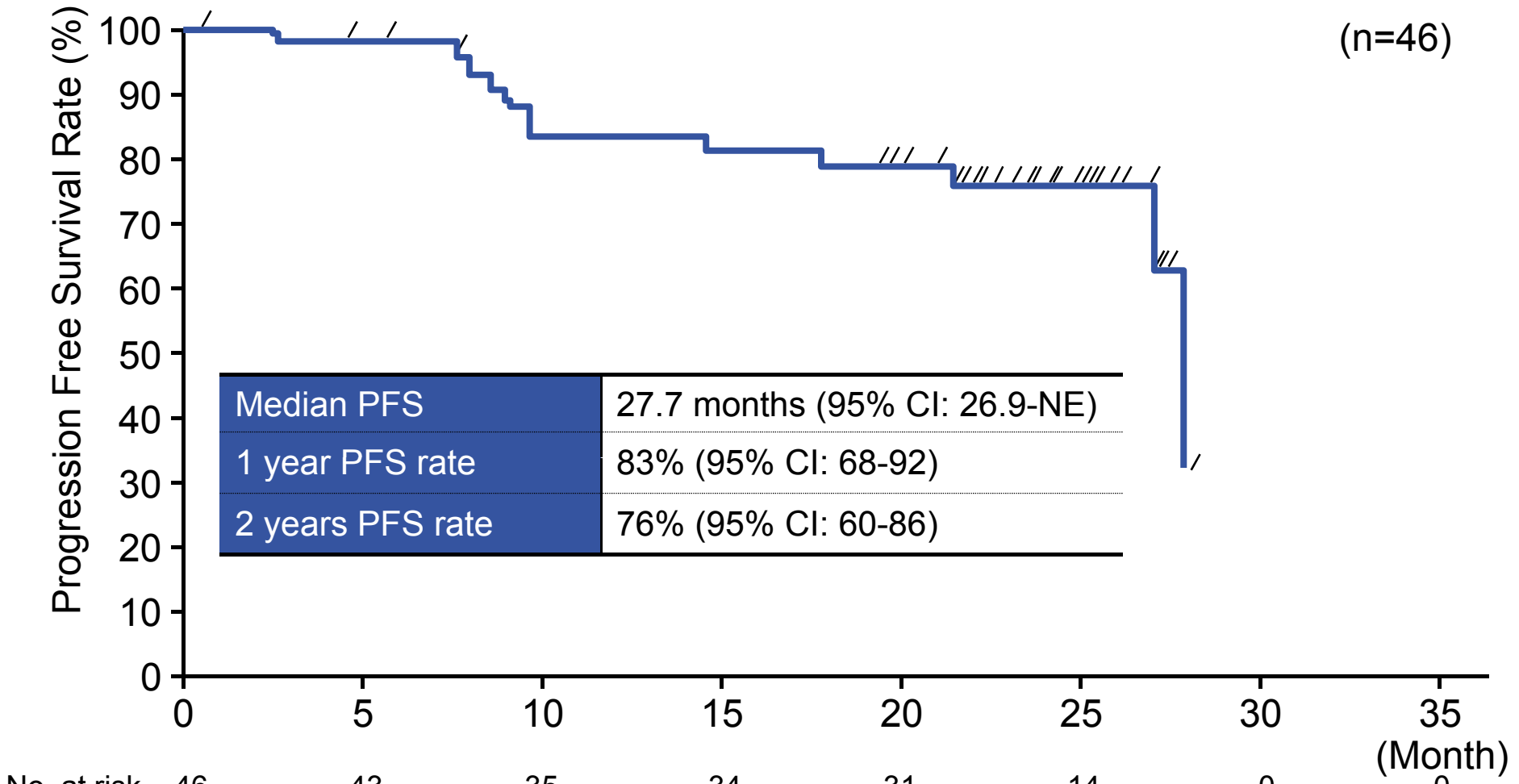
*All lesions had disappeared, nodal diseases were normalized RECIST1.1

Alectinib Phase I/II (AF-001JP)
Time to Tumor Volume Reduction Exceeding 30%



Seto T, et al. Lancet Oncol 2013;14(7): 590-8

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



2014/1/31 Cutoff

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

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

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

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

No AE over Grade4

Alectinib Phase I/II (AF-001JP)
Safety (Visual Disorder, Gastrointestinal Dysfunction)

(n=58)

Adverse Event (MedDRA ver. 13.1)		All Grade n(%)	Grade 3
Visual Disorder*	Blurred vision	1 (1.7%)	0
	Visual impairment	1 (1.7%)	0
Gastrointestinal Dysfunction	Nausea	9 (15.5%)	0
	Diarrhea	5 (8.6%)	0
	Vomiting	1 (1.7%)	0

*Seto T, et al. Lancet Oncol 2013;14(7): 590-8.

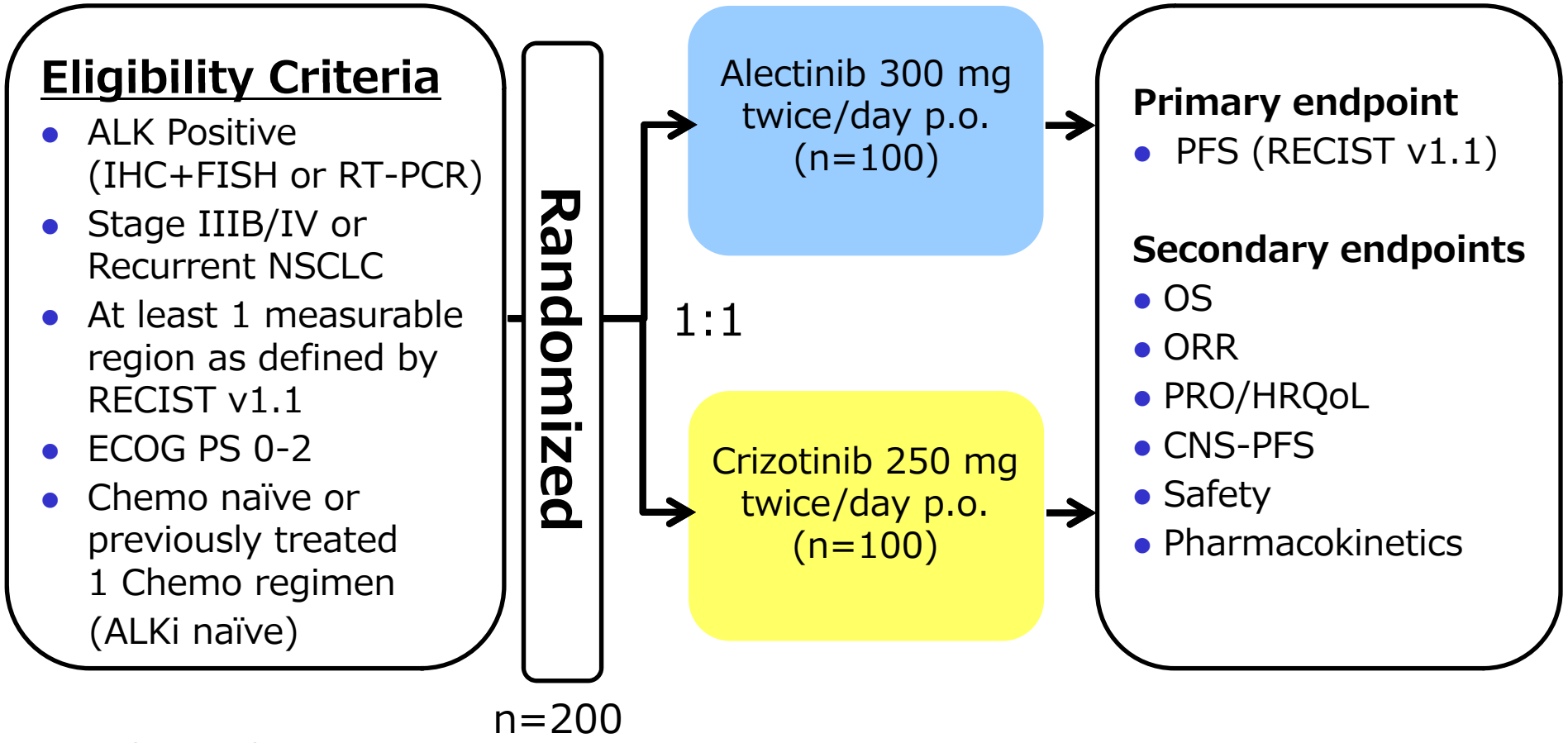
Alectinib Phase I/II (AF-001JP) Summary of Phase II part

- 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)



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.

ALECENSA®

Contents

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®.

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).

ALECENSA®

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)

Objective of the surveillance	To investigate the following aspects of drug use in actual clinical practice 1. Detection of unexpected adverse drug reactions. 2. To understand the incidence of adverse drug reactions including interstitial lung disease and liver function disorder. 3. To discover factors that may affect the onset of adverse drug reactions 4. Information regarding efficacy
Priority survey items	Interstitial lung disease, liver function disorder, and decreased neutrophil count/decreased white blood cell count
Subject to surveillance	**All patients administered ALECENSA®** during the enrollment period
Target number of patients	**1,000 patients**
Scheduled enrollment period	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.)

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®.

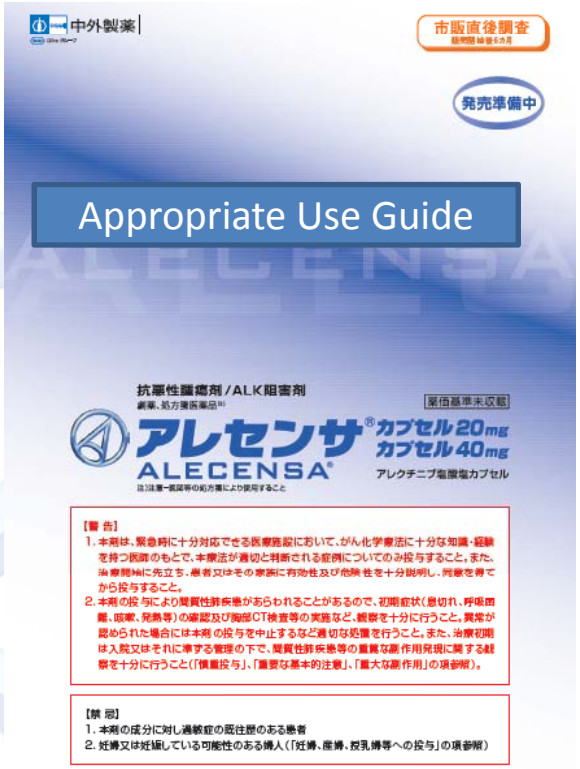
Physician requirements

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.

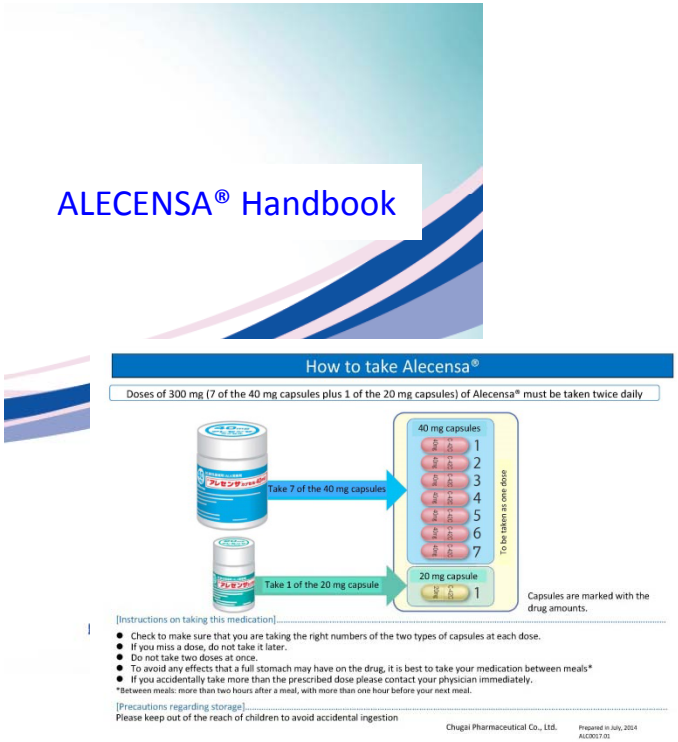
Implement Appropriate Distribution Control

Provision of information to promote appropriate use

For Healthcare Professionals



For Patients



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

Use of the ALECENSA® Emergency Contact Card

ALECENSA® Emergency Contact Card

[Front: Initial symptoms of clinically significant adverse reactions including ILD[1)]]

Alecensa® Emergency Contact Card

If you experience any of the following symptoms, please contact the hospital immediately.

□ **Shortness of breath, difficulty breathing, persistent coughing, or fever**
These may be the initial symptoms of interstitial lung disease.

□ **Fever, yellowing of the whites of the eyes or skin, brownish urine, nausea, vomiting, abdominal bloating, loss of appetite, feeling listless**
These may be the initial symptoms of impaired liver function

□ **Chills and Fever**
These may be the initial symptoms of neutropenia and leucopenia (decreased white blood cells)

□ **Sudden severe stomach pain**
This may be the initial symptoms of gastrointestinal perforation (a hole in the digestive tract)

□ **Chest pains, feeling of tightness, leg swelling and pain, shortness of breath, difficulty breathing.**
These may be the initial symptoms of a blood clot (thromboembolism)

Chugai Pharmaceutical Co., Ltd.

[Back: Emergency contact details]

■ **Emergency Contact Information**

Medical Institution:

Hospital phone number:

Clinical Department:

Attending physician:

Patient Registration Card No.:

Name:

Phone Number:

Prepared in July, 2014

ALC0010.01

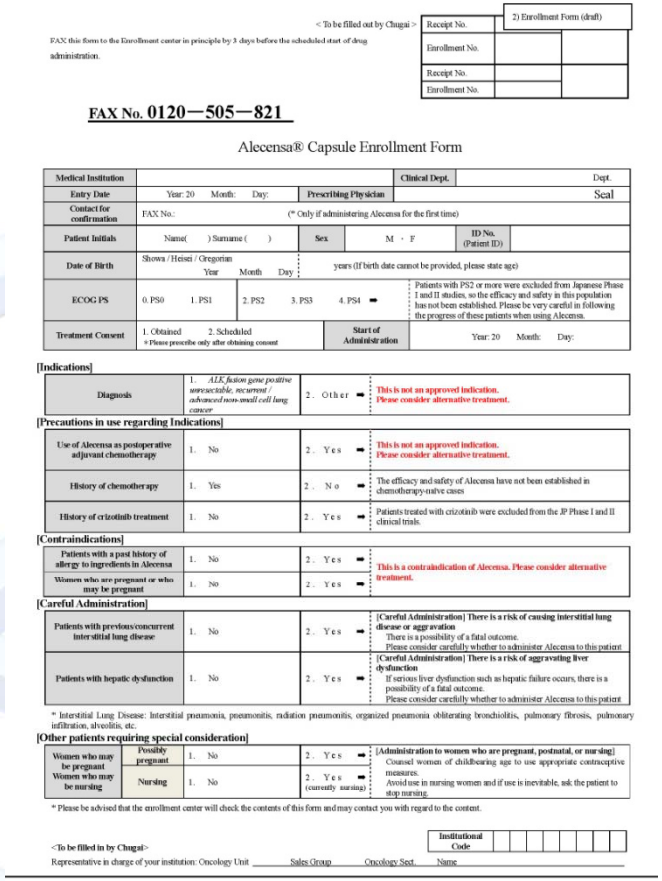
Business Card size (57mm x 88mm)

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.



< To be filled out by Chugai >

2) Enrollment Form (draft)

Receipt No.	
Enrollment No.	
Receipt No.	
Enrollment No.	

FAX this form to the Enrollment center in principle by 3 days before the scheduled start of drug administration.

FAX No. 0120—505—821

Alecensa® Capsule Enrollment Form

Medical Institution		Clinical Dept.	Dept.
Entry Date	Year: 20 Month: Day:	Prescribing Physician	Seal
Contact for confirmation	FAX No.: (* Only if administering Alecensa for the first time)		
Patient Initials	Name( ) Surname ( )	Sex	M · F
		ID No. (Patient ID)	
Date of Birth	Showa / Heisei / Gregorian Year Month Day	years (If birth date cannot be provided, please state age)	
ECOG PS	0. PS0 1. PS1 2. PS2 3. PS3 4. PS4 ➡	Patients with PS2 or more were excluded from Japanese Phase I and II studies, so the efficacy and safety in this population has not been established. Please be very careful in following the progress of these patients when using Alecensa.	
Treatment Consent	1. Obtained 2. Scheduled * Please prescribe only after obtaining consent	Start of Administration	Year: 20 Month: Day:

[Indications]

Diagnosis	1. *ALK fusion gene positive unresectable, recurrent / advanced non-small cell lung cancer*	2. Other ➡	This is not an approved indication. Please consider alternative treatment.

[Precautions in use regarding Indications]

Use of Alecensa as postoperative adjuvant chemotherapy	1. No	2. Yes ➡	This is not an approved indication. Please consider alternative treatment.
History of chemotherapy	1. Yes	2. No ➡	The efficacy and safety of Alecensa have not been established in chemotherapy-naïve cases
History of crizotinib treatment	1. No	2. Yes ➡	Patients treated with crizotinib were excluded from the JP Phase I and II clinical trials.

[Contraindications]

Patients with a past history of allergy to ingredients in Alecensa	1. No	2. Yes ➡	This is a contraindication of Alecensa. Please consider alternative treatment.
Women who are pregnant or who may be pregnant	1. No	2. Yes ➡	

[Careful Administration]

Patients with previous/concurrent interstitial lung disease	1. No	2. Yes ➡	[Careful Administration] There is a risk of causing interstitial lung disease or aggravation There is a possibility of a fatal outcome. Please consider carefully whether to administer Alecensa to this patient
Patients with hepatic dysfunction	1. No	2. Yes ➡	[Careful Administration] There is a risk of aggravating liver dysfunction If serious liver dysfunction such as hepatic failure occurs, there is a possibility of a fatal outcome. Please consider carefully whether to administer Alecensa to this patient

* Interstitial Lung Disease: Interstitial pneumonia, pneumonitis, radiation pneumonitis, organized pneumonia obliterating bronchiolitis, pulmonary fibrosis, pulmonary infiltration, alveolitis, etc.

[Other patients requiring special consideration]

Women who may be pregnant / Women who may be nursing	Possibly pregnant	1. No	2. Yes ➡	[Administration to women who are pregnant, postnatal, or nursing] Counsel women of childbearing age to use appropriate contraceptive measures. Avoid use in nursing women and if use is inevitable, ask the patient to stop nursing.
	Nursing	1. No	2. Yes ➡ (currently nursing)	

* Please be advised that the enrollment center will check the contents of this form and may contact you with regard to the content.

Institutional Code	

<To be filled in by Chugai>

Representative in charge of your institution: Oncology Unit ____ Sales Group ____ Oncology Sect. ____ Name ____

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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