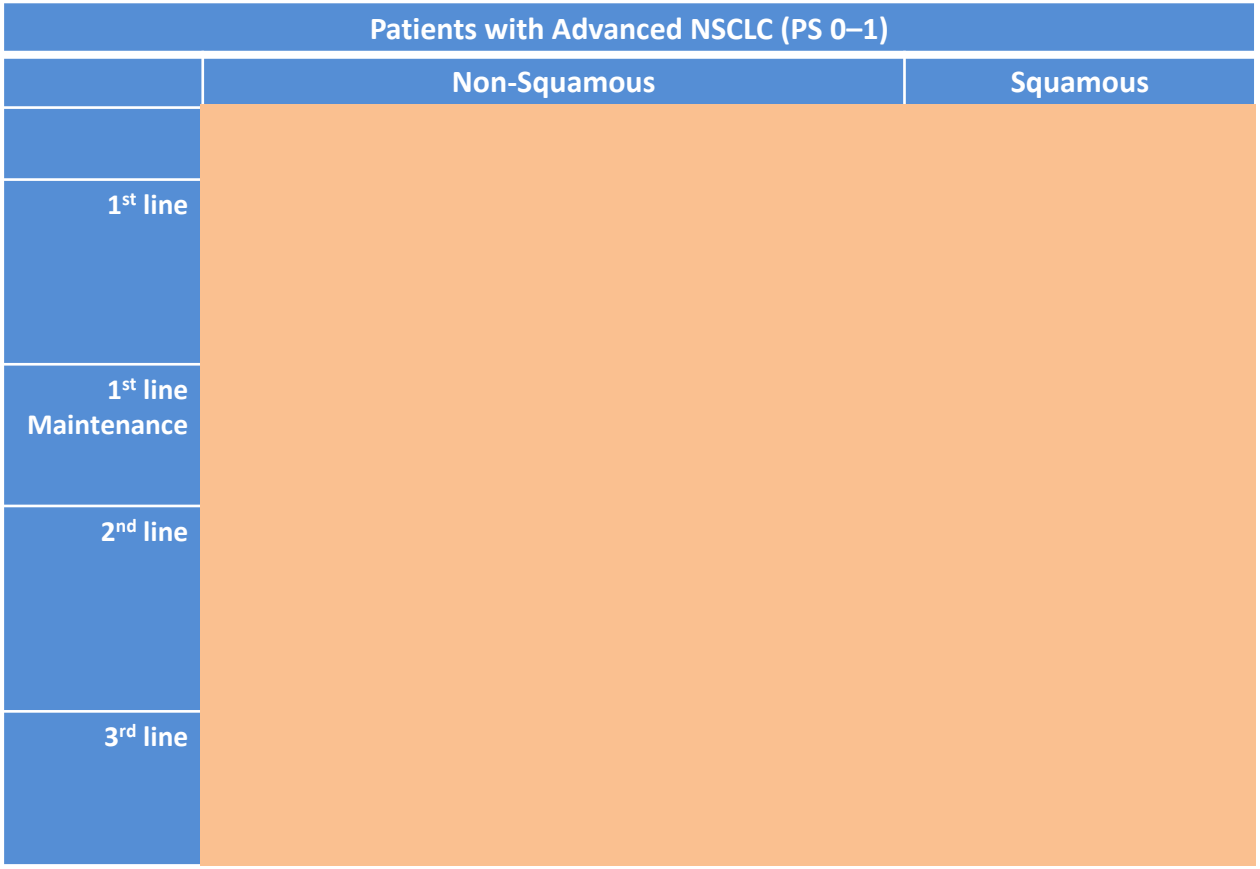
Case Oriented Clinical Applications of Lung Cancer

ALK Positive Patients

In-Jae Oh

Chonnam National University Hwasun Hospital

Compartmental Treatment Paradigm: Present ~ Near Future



Checkpoint does not include ipilimumab

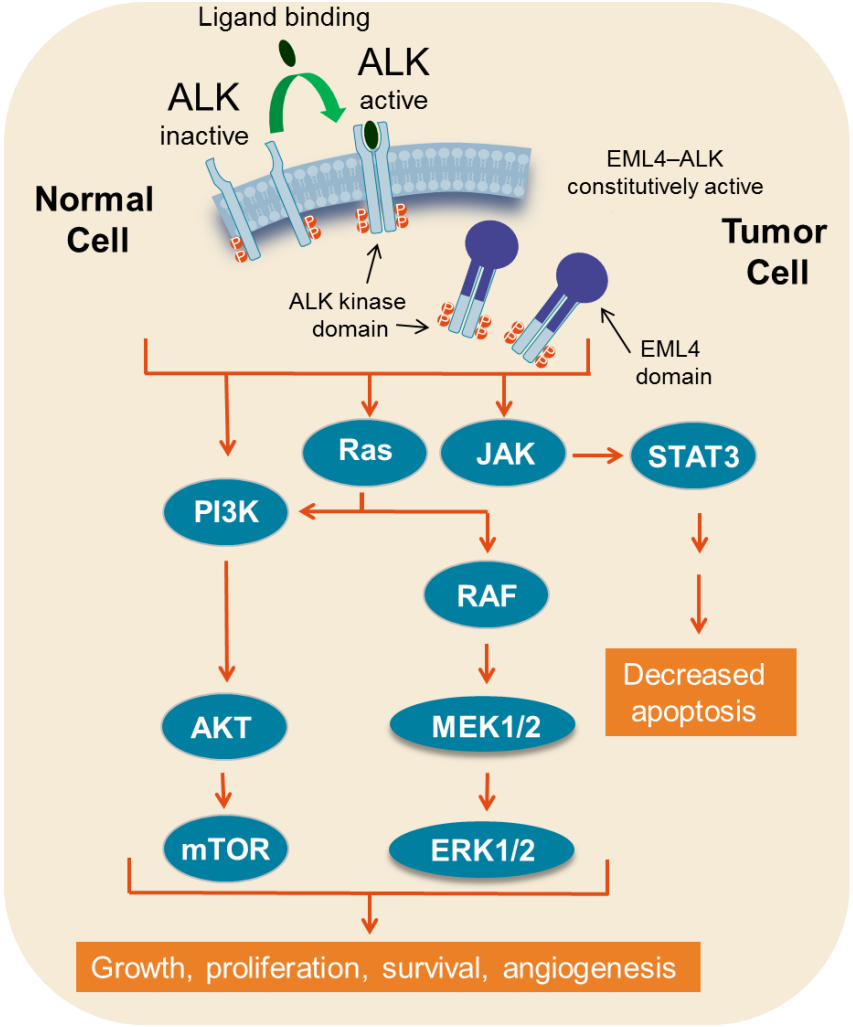
Modified from Gandara DR, et al. International Lung Cancer Congress 2016
Gandara DR, et al. *Clin Lung Cancer* (submitted)

CONTENTS

- Characteristics of EML4-ALK rearrangement
- Treatment of ALK positive patients
- Monitoring during ALK targeted therapy

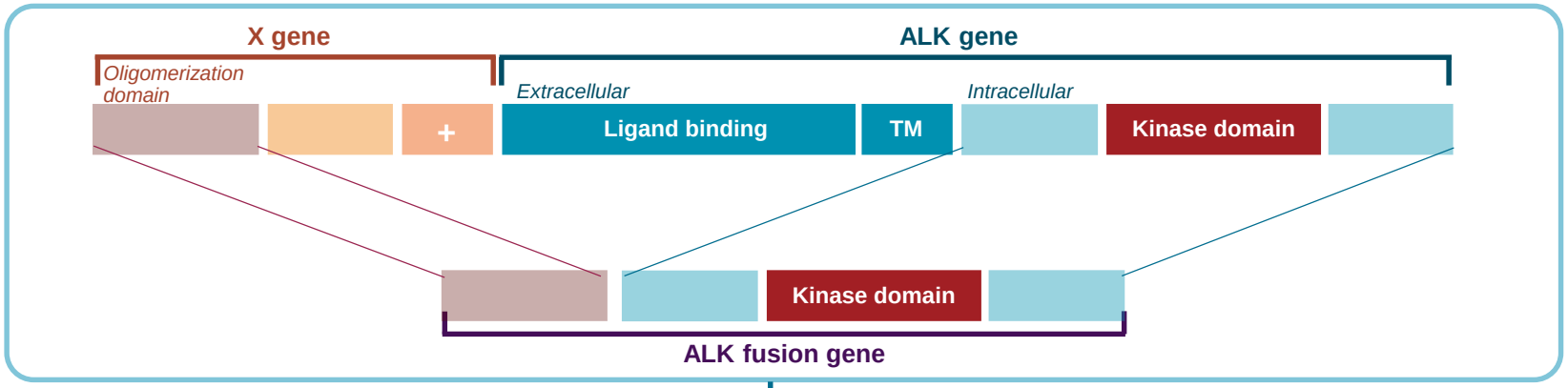
ALK+ NSCLC: Role of ALK as a Malignant Driver

- ALK is a receptor tyrosine kinase of the insulin receptor superfamily[1]
  - Expressed in neural tissue during early development but not normally expressed thereafter[2]
- ALK signaling is overactivated in NSCLC[2,3]
  - *ALK* gene rearrangement is the most common cause[3]
  - *EML4–ALK* fusion is the predominant rearrangement in Lung Cancer, and results in constitutive ALK activity that drives malignant transformation[3,4]



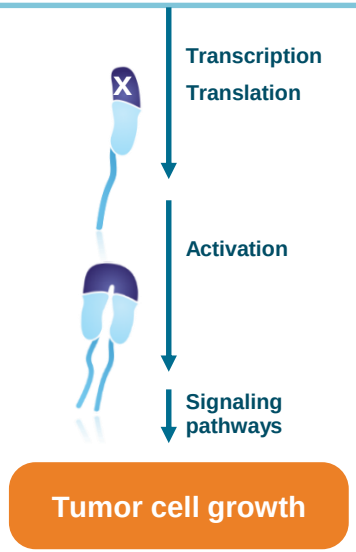
1. Stoica GE, *et al. J Biol Chem* 2001;276:16772–16779; 2. Ardini E, Galvani A. *Front Oncol* 2012;2:17; 3. Barreca A, *et al. J Mol Endocrinol* 2011;47:R11–R23; 4. Shaw AT, Engelman JA. *J Clin Oncol* 2013;31:1105–1111.

Human ALK Gene Rearrangements



- Genetic rearrangements of DNA can create novel fusion proteins[1,2]
- In the case of ALK, genetic rearrangements result in the intracellular KD of ALK fusing to the oligomerization domain of a fusion partner (X)[1,2]

"X" represents the oligomerization domain of any fusion partner that fuses with ALK.

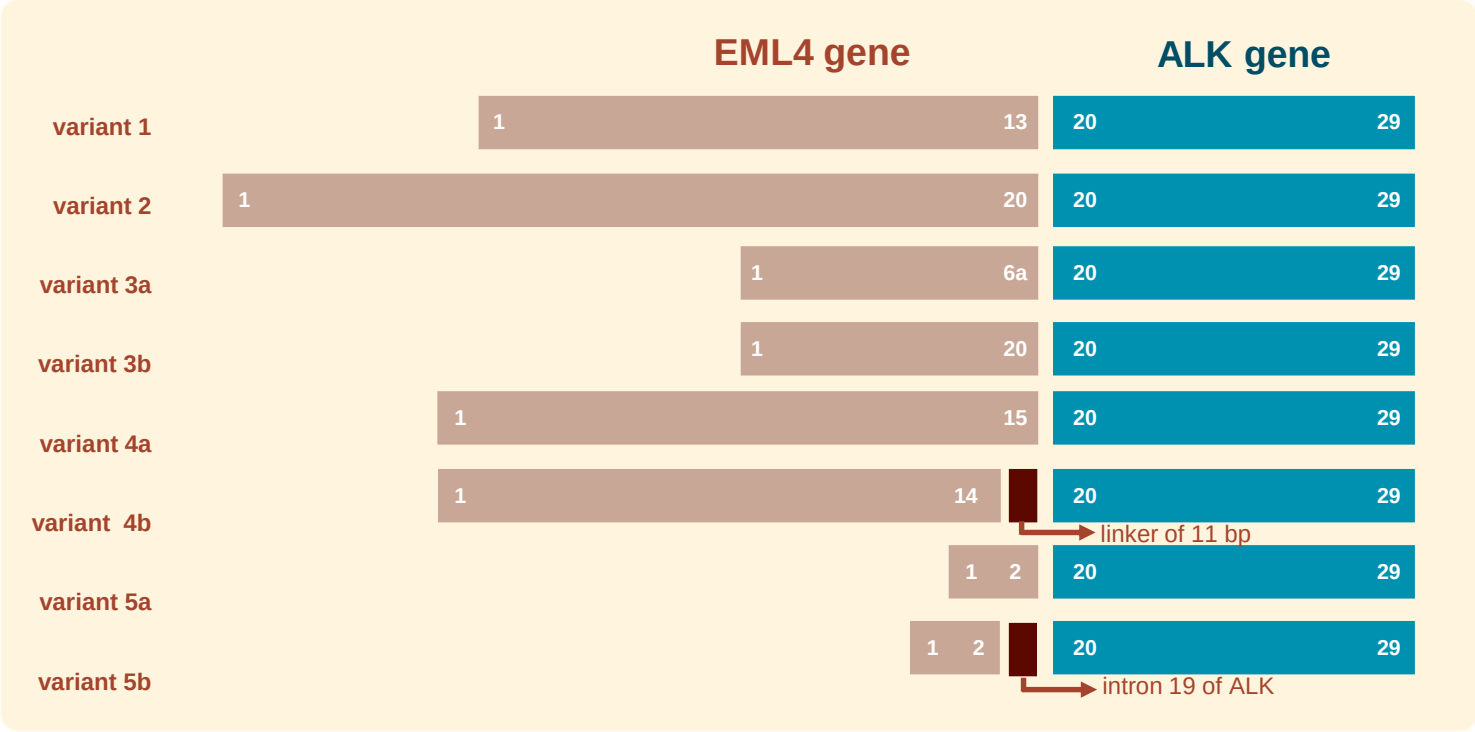


- The resulting fusion protein does not have a TM domain; therefore, it is found free in the cytoplasm[3]
- The oligomerization domains cause the new fusion proteins to dimerize independently of ligand binding[1,3]
- Dimerization activates the KDs of ALK, in turn activating signaling pathways that promote tumor cell growth[1]

1. Ardini E, et al. *Cancer Lett.* 2010;299:81-94.
2. Cheng M, Ott GR. *Anticancer Agents Med Chem.* 2010;10:236-249.
3. Shaw AT and Solomon B. *Clin Cancer Res.* 2011;17:2081-2086.

EML4-ALK Fusion Protein Variants

- A number of EML4-ALK fusion variants have been reported; all contain the same intracellular region of ALK but contain different truncations of EML4[1,2]
  - Variants 1, 2, and 3a/3b comprise 33%, 10%, and 29% of the fusion variants, respectively[3]
  - In vitro, different EML4-ALK fusion variants demonstrated varying levels of sensitivity to ALK inhibitors[3]
  - However, there has been no association detected to date between EML4-ALK variant and response to ALK targeted therapy in clinical trials[4]



Chromosome 2. Numbers = exon number.

1. Ardini E, et al. *Cancer Lett.* 2010;299:81-94. 2. Perner S, et al. Atlas of genetics and cytogenetics in oncology and haematology. July 2009. http://AtlasGeneticsOncology.org/Genes/EML4ID44353ch2p21.html. Accessed October 14, 2013. 3. Heuckmann JM, et al. *Clin Cancer Res.* 2012;18:4479-4481. 4. Crystal AS and Shaw AT. *Clin Cancer Res.* 2012;18:4479-4481.

Q1. 어떤 폐암 환자에서 ALK 재배열 검사를 해야 할까요?

1) 비흡연 여성

2) 젊은 환자(60세 이하)

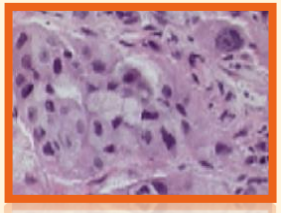
3) 선암으로 확인된 환자

4) EGFR 돌연변이 없는 환자

5) 상기 모든 경우에 검사 가능

Common Characteristics of ALK+ NSCLC

- ALK rearrangement frequency varies with histology, smoking status, and age



Histology

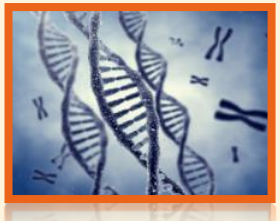
- ALK rearrangement is more common in adenocarcinoma[1,2]
- Presence of signet ring cell component has been reported as a prominent feature of EML4-ALK+ NSCLC[3]

Smoking history

- Associated with a history of never or light smoking[4,5]

Age

- Younger median age at diagnosis than for patients without ALK rearrangement (54 vs 64 years)[2,5]

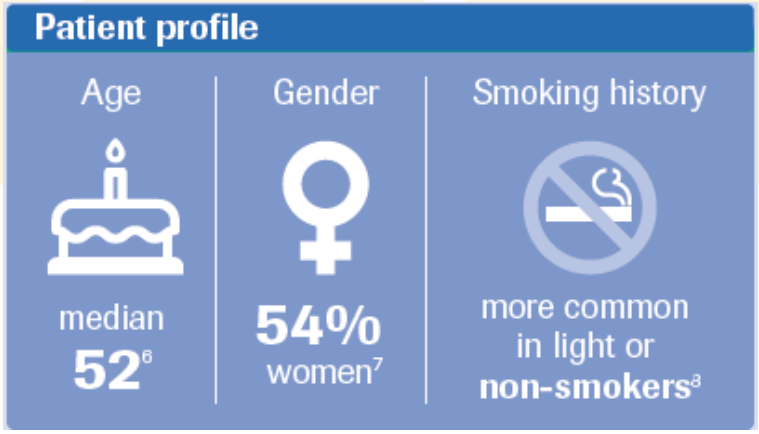


Concurrent Mutations

- Usually occurs in the absence of EGFR or KRAS mutations[1, 4-5]

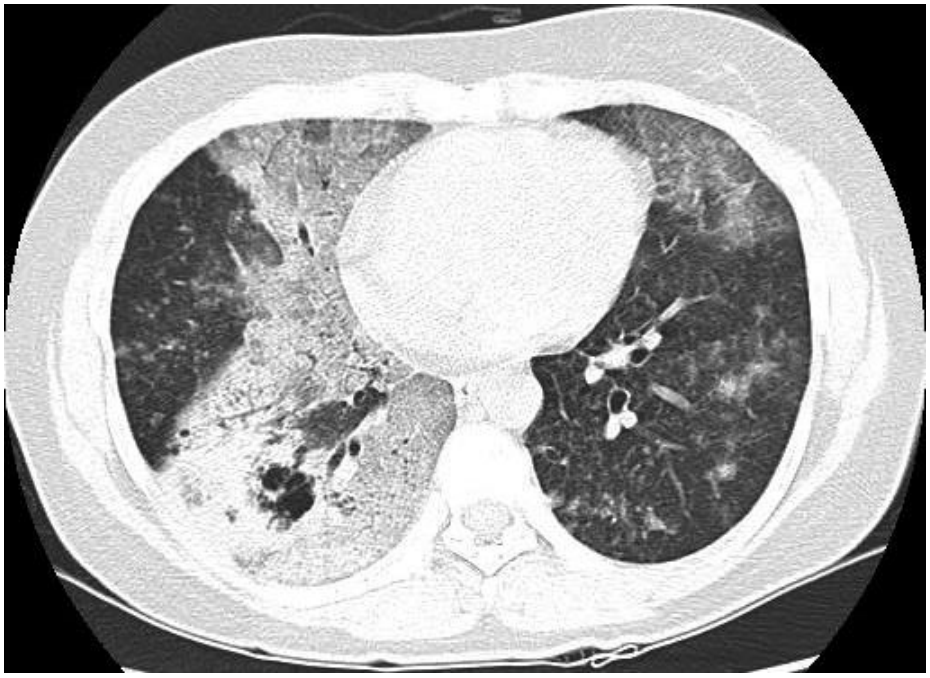
Sex

- ALK+ NSCLC occurs more commonly in females[6]



1. Inamura K, et al. *J Thorac Oncol.* 2008;3:13-17.
2. Shaw AT, Solomon B. *Clin Cancer Res.* 2011;17:2081-2086.
3. Ou SH. *J Thorac Oncol*. 2010;5(4):420-427.
4. Wong DW, et al. *Cancer.* 2009;115:1723-1733.
5. Rodig SJ, et al. *Clin Cancer Res.* 2009;15:5216-5223.
6. Li Y, et al. *PLoS ONE.* 2013;8:e52093.

ALK+NSCLC are sensitive to treatment with Crizotinib



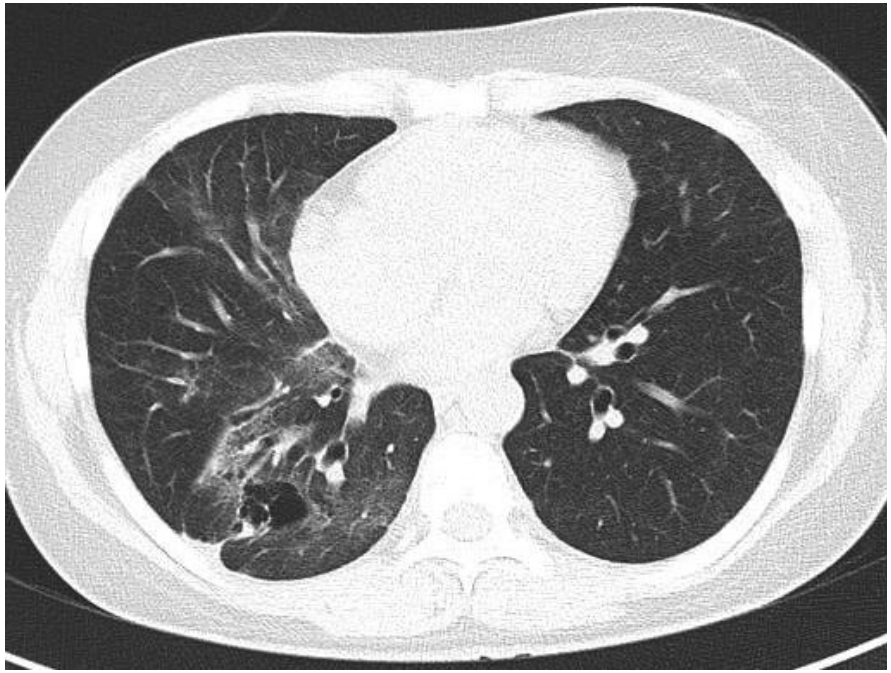
42/F, ADC, T4 N2 M1a

1-AP 2014 Jun~ 15 Jan 10x
2-IRESSA: 2015 Jan~Mar
3-Gem: 2015. Mar 3x PD

ALK-IHC (-),

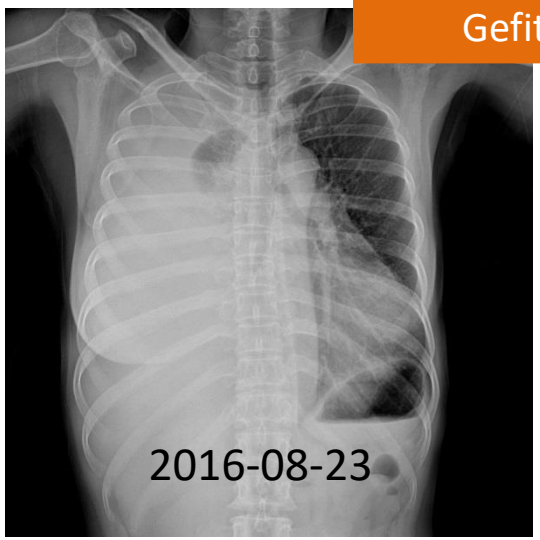
ALK-FISH positive

→ 4-Crizotinib
since Jun 4 2015

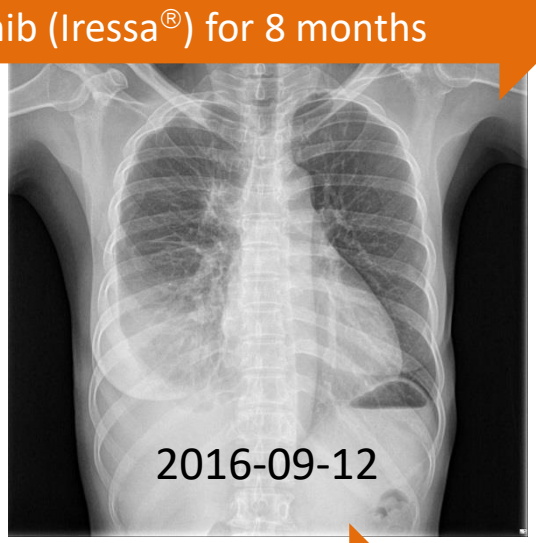


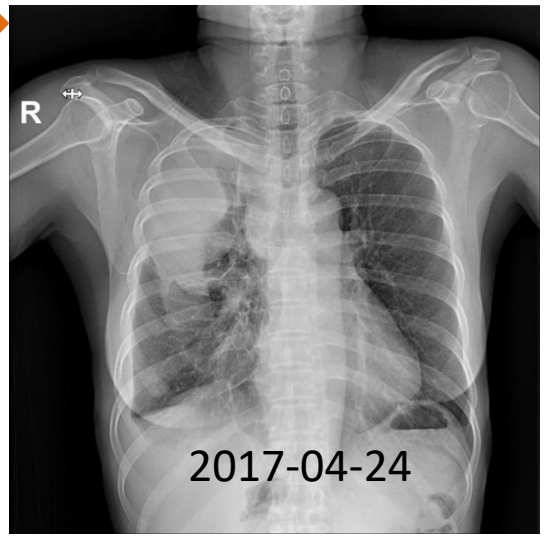
56/F, ADC IV (T2aN3M1b) - pleura, sacral mets

- EGFR PNA clamping from RUL mass bx: L858R
- ALK FISH from RUL mass bx: (+), 20%

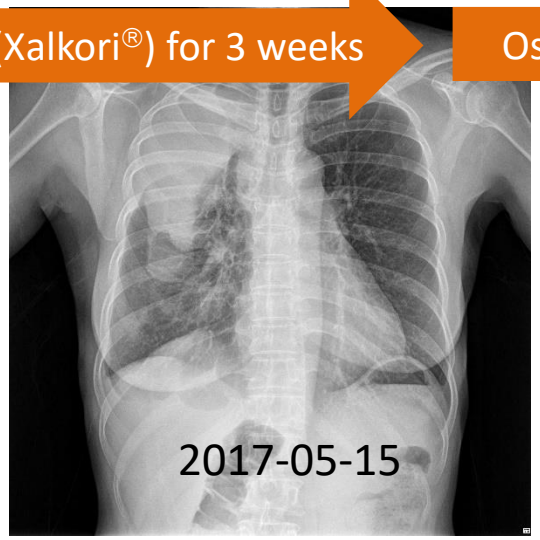


Gefitinib (Iressa®) for 8 months





Crizotinib (Xalkori®) for 3 weeks



Osimertinib (Tagrisso®) for 2 months

ALK+ disease is a distinct subset of NSCLC

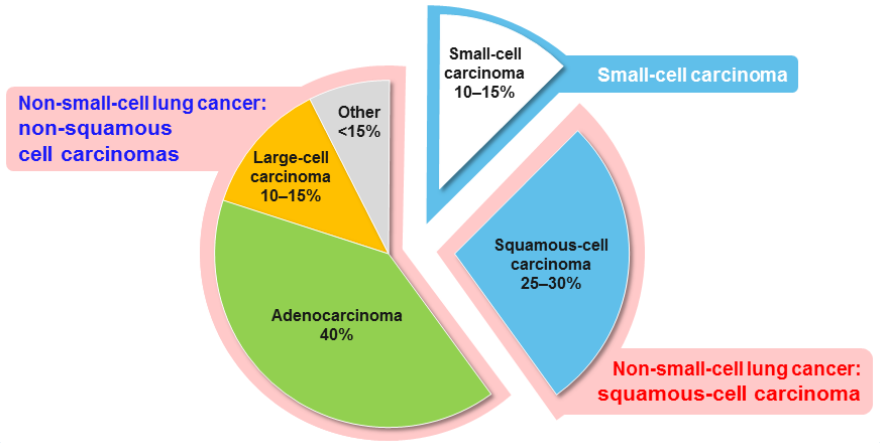
ALK+ disease occurs in ~5% of patients with advanced NSCLC[1–5]

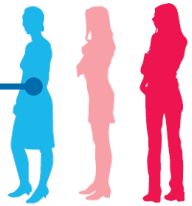
More than 75,000 patients per year diagnosed[7]

The incidence of *ALK*+ NSCLC is higher in

- Patients with non-squamous histology[2,8]
- Never or former smokers[2,8]
- Younger patients[2,8]
- Females[2]
- Patients who do not have *EGFR* or *KRAS* mutations[2,8]

Histological classification of lung cancer[6]





Clinical characteristics do not always predict the presence of *ALK*+ NSCLC[9,10]

ALK = anaplastic lymphoma kinase
EGFR = epidermal growth factor receptor
NSCLC = non-small cell lung cancer

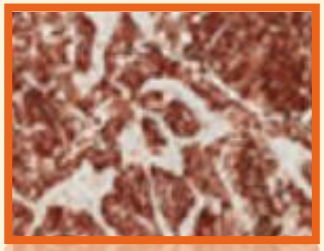
1. Dearden, et al. Ann Oncol 2013; 2. Gridelli, et al. Cancer Treat Rev 2014
3. Hallberg, et al. Nat Rev Cancer 2013; 4. Rikova, et al. Cell 2007
5. Soda, et al. Nature 2007; 6. American Cancer Society 2013
7. Torre, et al. CA Cancer J Clin 2015; 8. Perez, et al. Lung Cancer 2014
9. Lindeman, et al. J Thorac Oncol 2013; 10. Leighl, et al. J Clin Oncol 2014

ALK Diagnostic Techniques

- Each can be done using primary or metastatic tumor tissue, pleural fluid, or cytologic FFPE samples

FISH[1]

- Fluorescent probes are used to label and detect specific regions on a gene
- Samples are viewed under a microscope

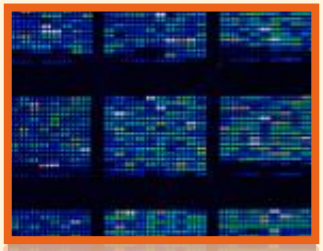


IHC[2]

- Antibodies are used to detect specific proteins expressed by cells
- A chemical reaction generates a color deposit on cells which bind the antibody
- The cells may be identified under a microscope

RT-PCR[3]

- Relatively large numbers of copies of DNA produced from minute quantities of RNA source material



Next-generation sequencing (NGS)[4]

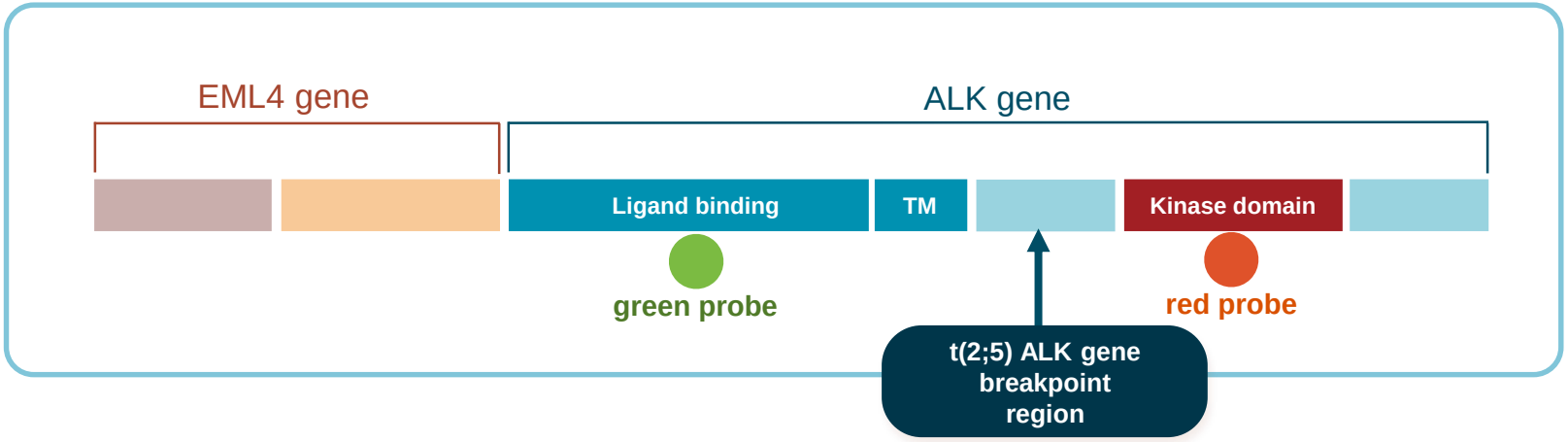
- Uses micro- and nanotechnologies to run massively parallel sequencing

1. Vincent MD, *et al. Curr Oncol.* 2012;19:S33-S44.
2. Ramos-Vara JA. *Vet Pathol.* 2005;42:405-426.
3. Peake I. *J Clin Pathol.* 1989;42:673-676.
4. Grada A, Weinbrecht K. *J Invest Dermatol*. 2013;133:e11.

Break Apart FISH Assay for NSCLC

- Fluorescent probes (green and red) are used to label different regions of the ALK gene on chromosome 2[1]
  - The red probe labels the KD of ALK (the region targeted by ALK inhibitors),[2] and the green probe labels the ligand-binding domain[3]
- Samples are viewed with a microscope, and the number of cells demonstrating an abnormal pattern of fluorescent signals is counted[1,2]
- If ≥ **15%** of ≥ 50 cell nuclei show ALK rearrangement by FISH, the tumor is classified as ALK+[1]
  - Borderline results (10%-20%+ cells) occur in about 8% of cases[3]

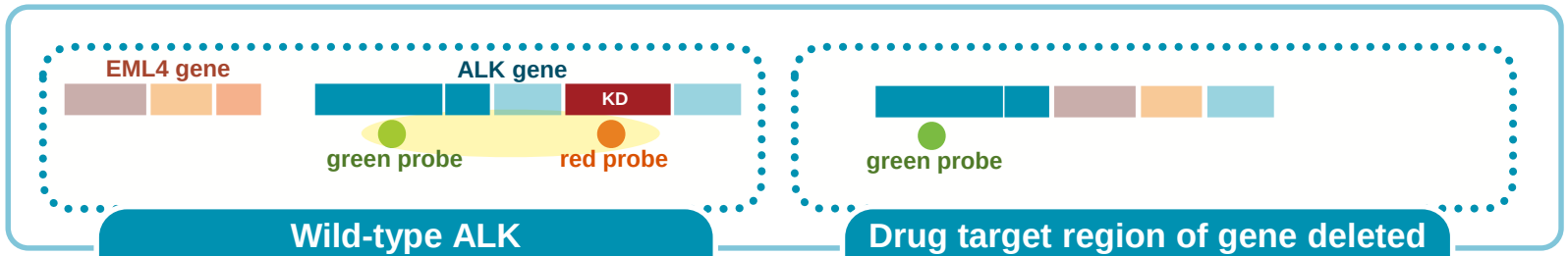
Labeling of the ALK gene[3]



1. Vincent MD, et al. *Curr Oncol.* 2012;19:S33-S44.
2. Abbott Molecular. Vysis ALK Break Apart FISH Probe Kit product information. 2011. http://www.abbottmolecular.com/static/cms_workspace/pdfs/US/Vysis_ALK_FISH_Probe_Kit_PI.pdf. Accessed October 14, 2013.
3. Camidge DR, et al. *Cancer*. 2013;119:3968-3975.

Interpreting Results From the Vysis ALK Break Apart FISH Assay

Negative Result[1]

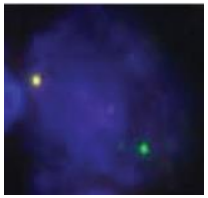


Wild-type ALK

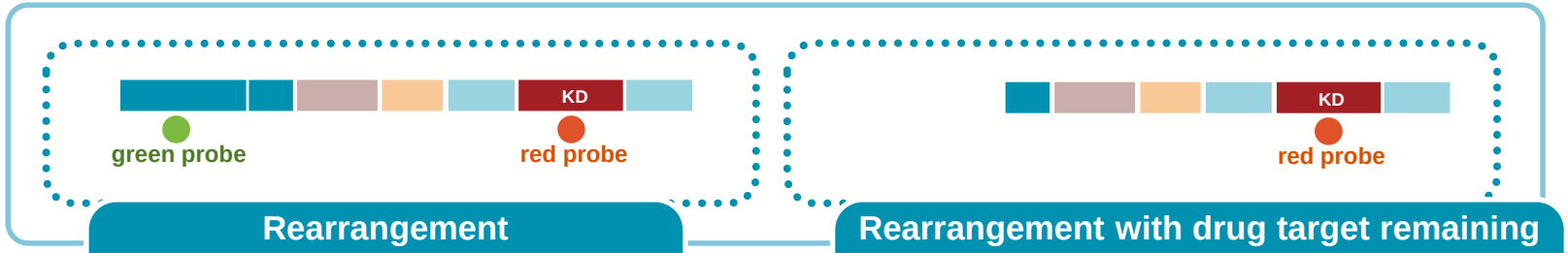
If the cells do not have an ALK rearrangement, then the red and green probes will be very close together and will appear yellow

Drug target region of gene deleted

A single green signal is considered negative because it indicates a deletion of the portion of ALK that is targeted by ALK inhibitors

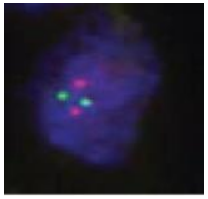


Positive Result[1]



Rearrangement

When the ALK gene is rearranged, the red and green colors are far enough away to be seen separately



Rearrangement with drug target remaining

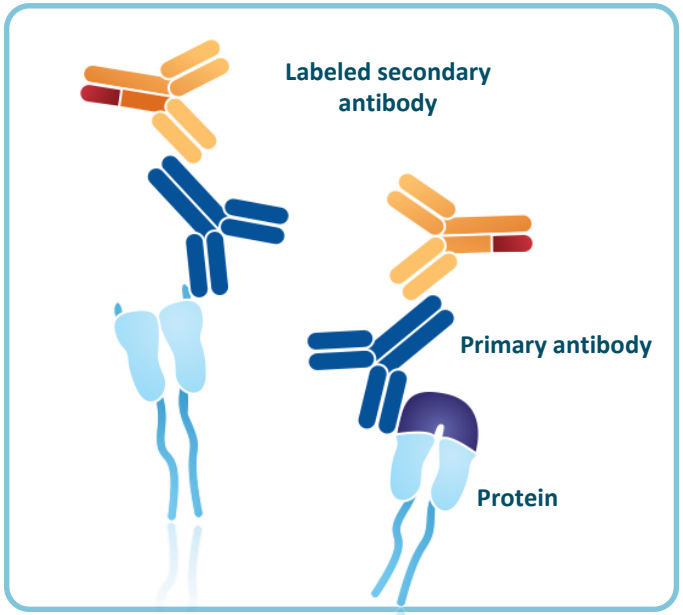
A single red signal indicates a deletion of the green part and is considered positive because the portion of ALK that is targeted by ALK inhibitors remains

1. Abbott Molecular. Vysis ALK Break Apart FISH Probe Kit product information. 2011. http://www.abbottmolecular.com/static/cms_workspace/pdfs/US/Vysis_ALK_FISH_Probe_Kit_PI.pdf. Accessed October 14, 2013.
2. Tsao, MS, et al, eds. *IASLC Atlas of ALK Testing in Lung Cancer*. 2013. https://www.iaslc.org/publications/iaslc-atlas-alk-testing-lung-cancer. Accessed May 28, 2014. (Images)

Immunohistochemistry (IHC)

- IHC is used to detect ALK protein expression; it does not directly identify the ALK gene rearrangement

- Anti-ALK (D5F3) rabbit monoclonal primary antibody is used to detect protein in FFPE NSCLC tissue stained on a **VENTANA** BenchMark XT or BenchMark GX IHC automated slide stainer
  - Available in more than 53 countries, including Europe and China[1,2]
  - The Ventana test is read as a positive or negative score[3] by a qualified pathologist[1]

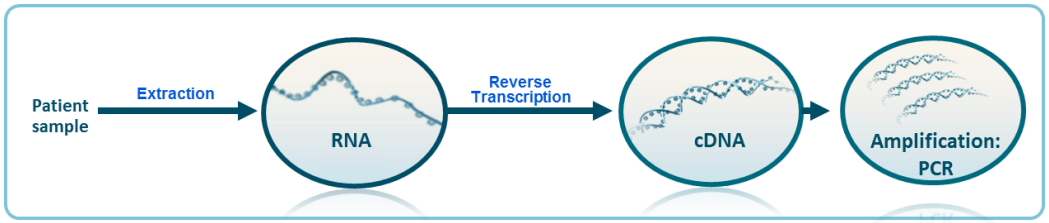


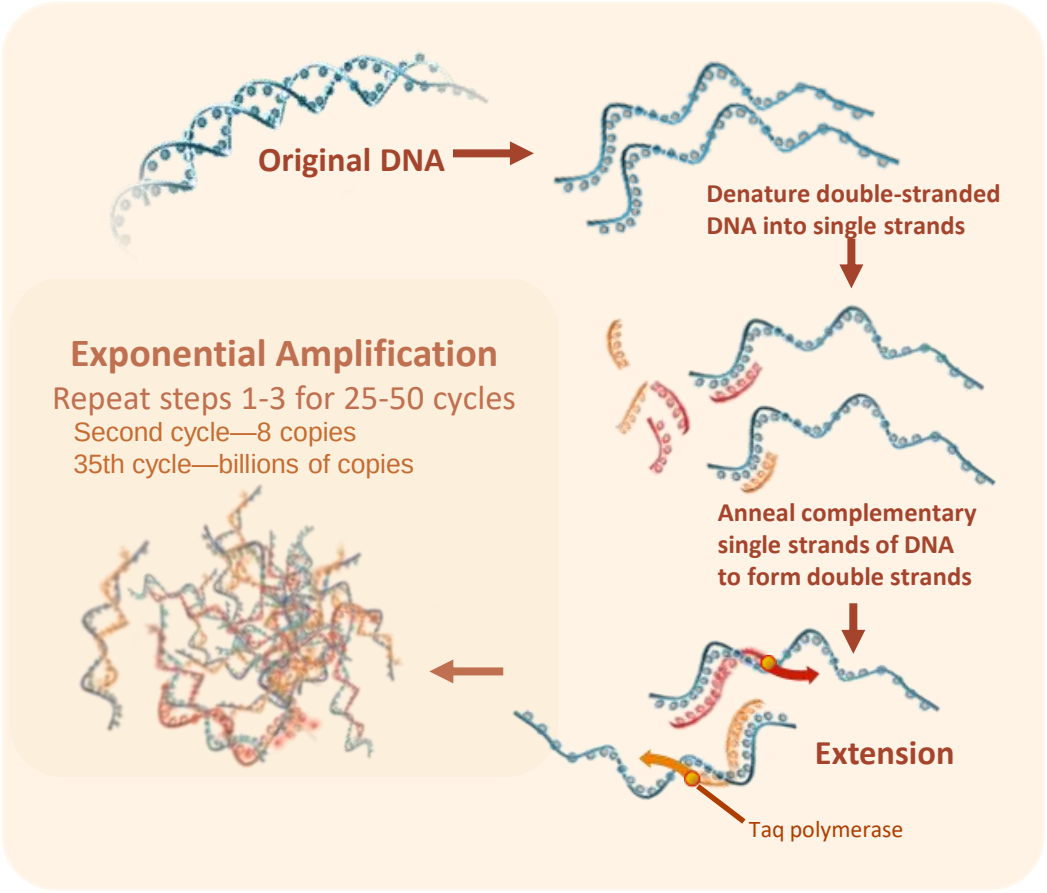
Clinical Interpretation	Staining Pattern	Staining Description
ALK positive		Presence of strong granular cytoplasm staining in tumor cells. Staining of nontumor cells should be excluded. Background staining of normal mucosa in NSCLC and necrotic tumor cells should be excluded.
ALK negative		Absence of strong granular cytoplasmic staining in tumor cells.

1. Ventana ALK Scoring *Interpretation Guide* for non-small cell lung carcinoma (NSCLC). 2012. http://www.uclad.com/newsletters/ALK-LUNG-IHC-INTERPRETATION-GUIDE.pdf. Accessed October 14, 2013.
2. Ventana [press release]. September 11, 2013. Accessed March 27, 2014.

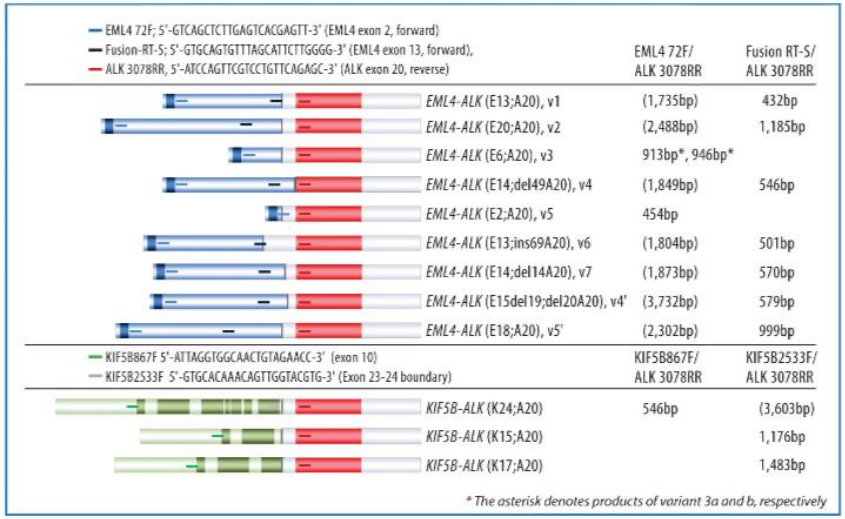
Polymerase Chain Reaction (PCR)

- PCR produces relatively large numbers of copies of DNA from minute quantities of source DNA or RNA material[1]





Primer Sites and Their Expected Product Lengths of Multiplex RT-PCR[2]



1. Peake I. *J Clin Pathol.* 1989;42:673-676.
2. Tsao, MS, et al, eds. *IASLC Atlas of ALK Testing in Lung Cancer*. 2013. https://www.iaslc.org/publications/iaslc-atlas-alk-testing-lung-cancer. Accessed May 28, 2014.

Q2. ALK FISH 양성 4병기 폐선암 환자의 1차 치료는?

1) Pemetrexed + cisplatin
2) Crizotinib (Xalkori™)
3) Ceritinib (Zykadia™)
4) Alectinib (Alecensa™)
5) All of above

ALK inhibitors (ALKi)

Approved	**Crizotinib**	**Ceritinib**	**Alectinib**
Breakthrough Therapy	**Brigatinib**		
Investigational	**Lorlatinib**	**Ensartinib**	**Entrectinib**

Current Treatment Algorithm for ALK+ NSCLC

1st generation ALKi → Progressive disease → **2nd generation ALKi**

Solomon & Soria, Annals of Oncology 2016 Soria ESMO 2016

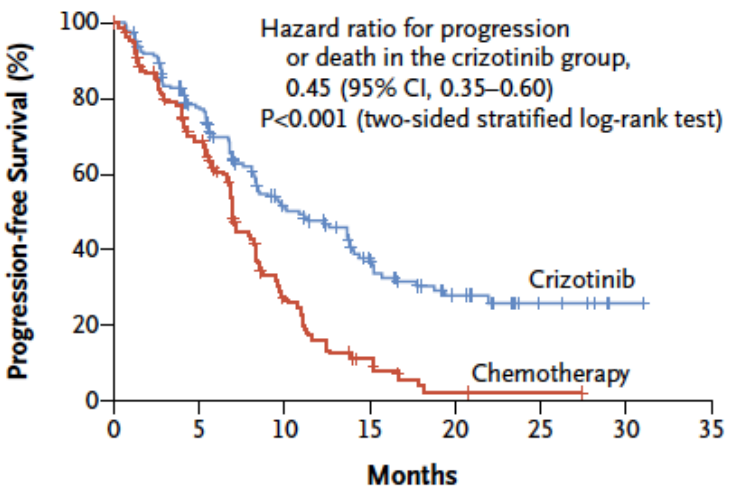
PROFILE 1014:
First-line crizotinib vs. chemotherapy

ORIGINAL ARTICLE

First-Line Crizotinib versus Chemotherapy in *ALK*-Positive Lung Cancer

Benjamin J. Solomon, M.B., B.S., Ph.D., Tony Mok, M.D.,

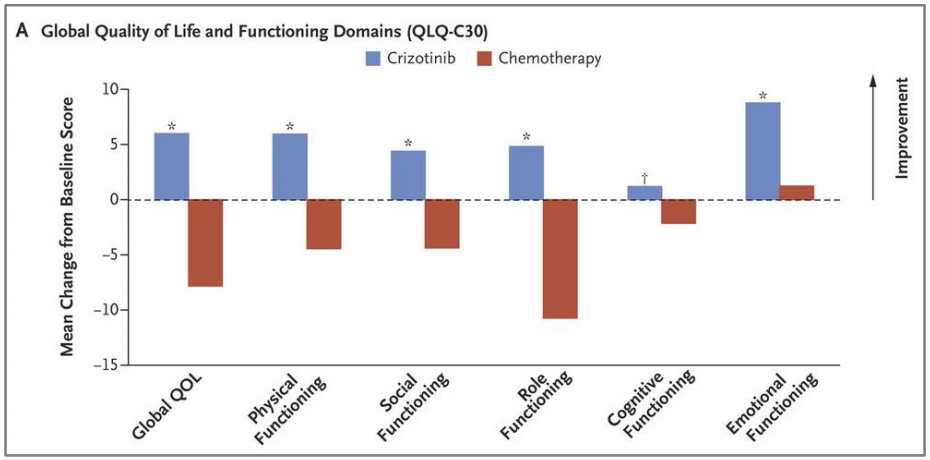
Progression-free Survival



PFS: 10.9 vs. 7.0 months

Table 2. Response to Treatment in the Intention-to-Treat Population.*

Response	Crizotinib (N=172)	Chemotherapy (N=171)
Type of response — no. (%)		
Complete response	3 (2)	2 (1)
Partial response	125 (73)	75 (44)
Stable disease	29 (17)	63 (37)
Progressive disease	8 (5)	21 (12)
Could not be evaluated†	7 (4)	10 (6)
Objective response rate — % (95% CI)‡	74 (67–81)	45 (37–53)



Solomon BJ, et al. N Engl J Med 2014;371:2167–77

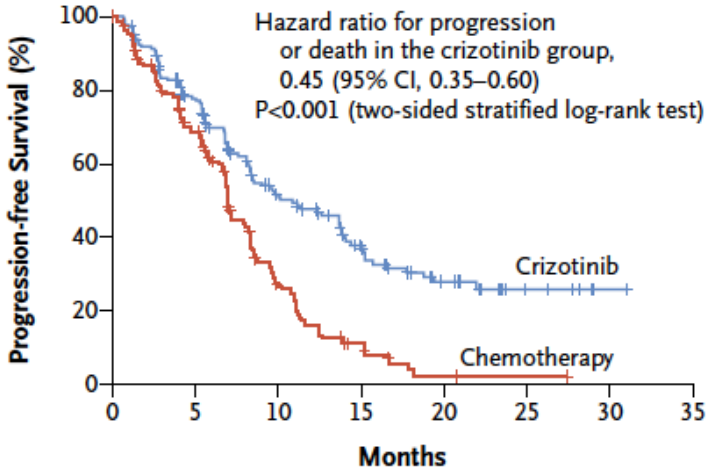
Crizotinib: benefit is higher in first-line vs. second-line

ORIGINAL ARTICLE

First-Line Crizotinib versus Chemotherapy in *ALK*-Positive Lung Cancer

Benjamin J. Solomon, M.B., B.S., Ph.D., Tony Mok, M.D.,

A Progression-free Survival



PFS: 10.9 months

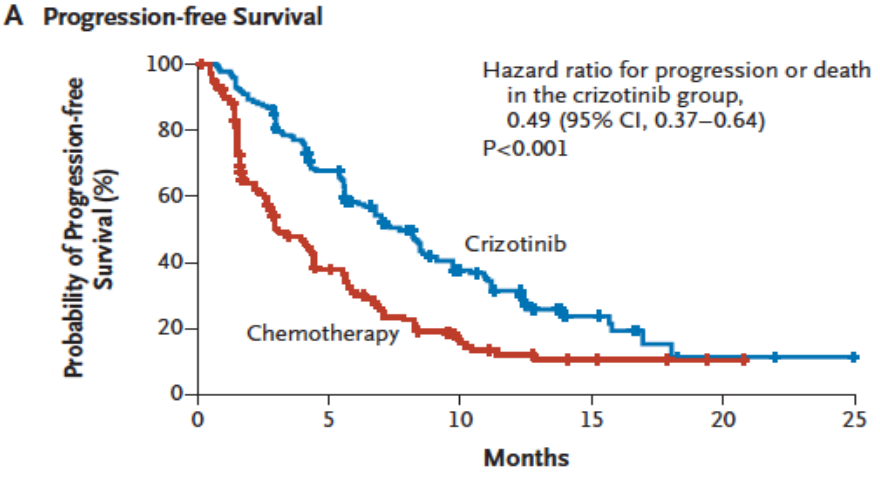
N Engl J Med 2014;371:23

ORIGINAL ARTICLE

Crizotinib versus Chemotherapy in Advanced *ALK*-Positive Lung Cancer

Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D.,
Kazuhiko Nakagawa, M.D., Ph.D., Takashi Seto, M.D., Lucio Crinó, M.D.,

A Progression-free Survival



PFS: 7.7 months

N Engl J Med 2013;368:2385

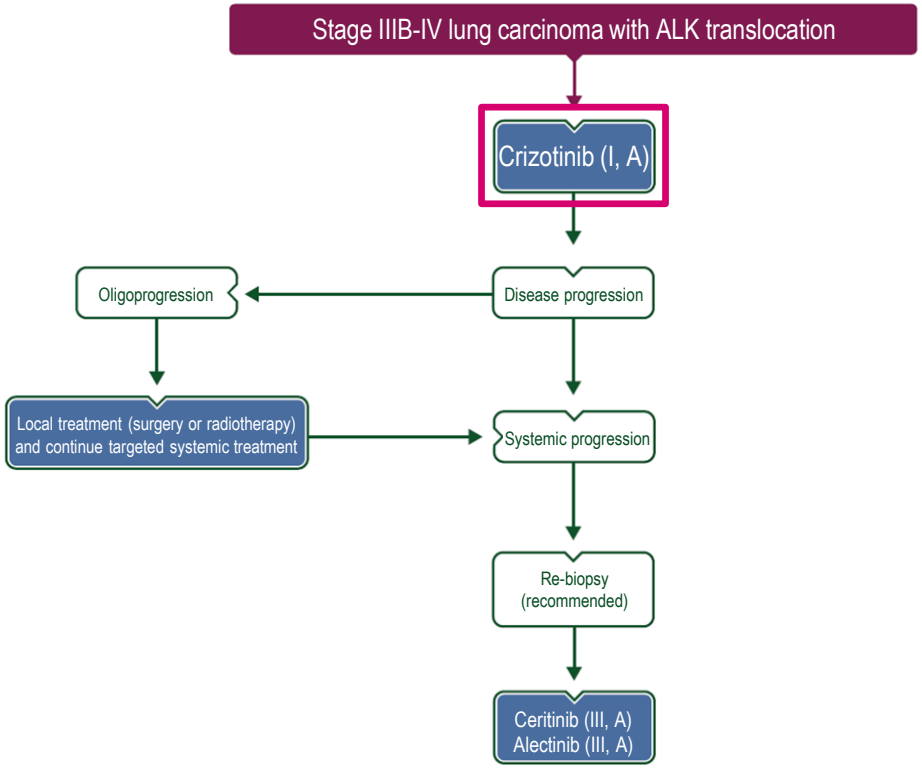
Crizotinib: today our standard in first-line

clinical practice guidelines

Annals of Oncology 27 (Supplement 5): v1–v27, 2016
doi:10.1093/annonc/mdw326

Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

S. Novello[1], F. Barlesi[2], R. Califano[3,4], T. Cufer[5], S. Ekman[6], M. Giaj Levra[7], K. Kerr[8], S. Popat[9], M. Reck[10], S. Senan[11], G. V. Simo[12], J. Vansteenkiste[13] & S. Peters[14] on behalf of the ESMO Guidelines Committee*



National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Small Cell Lung Cancer

Version 2.2017 — October 26, 2016

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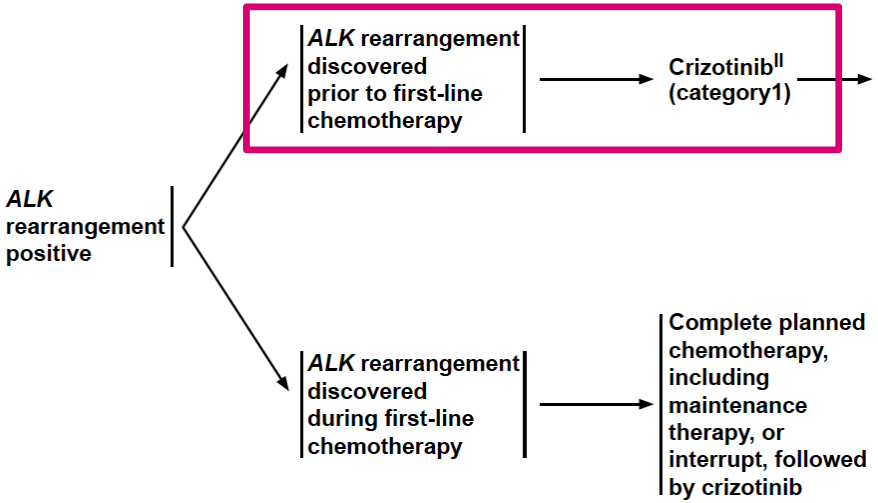
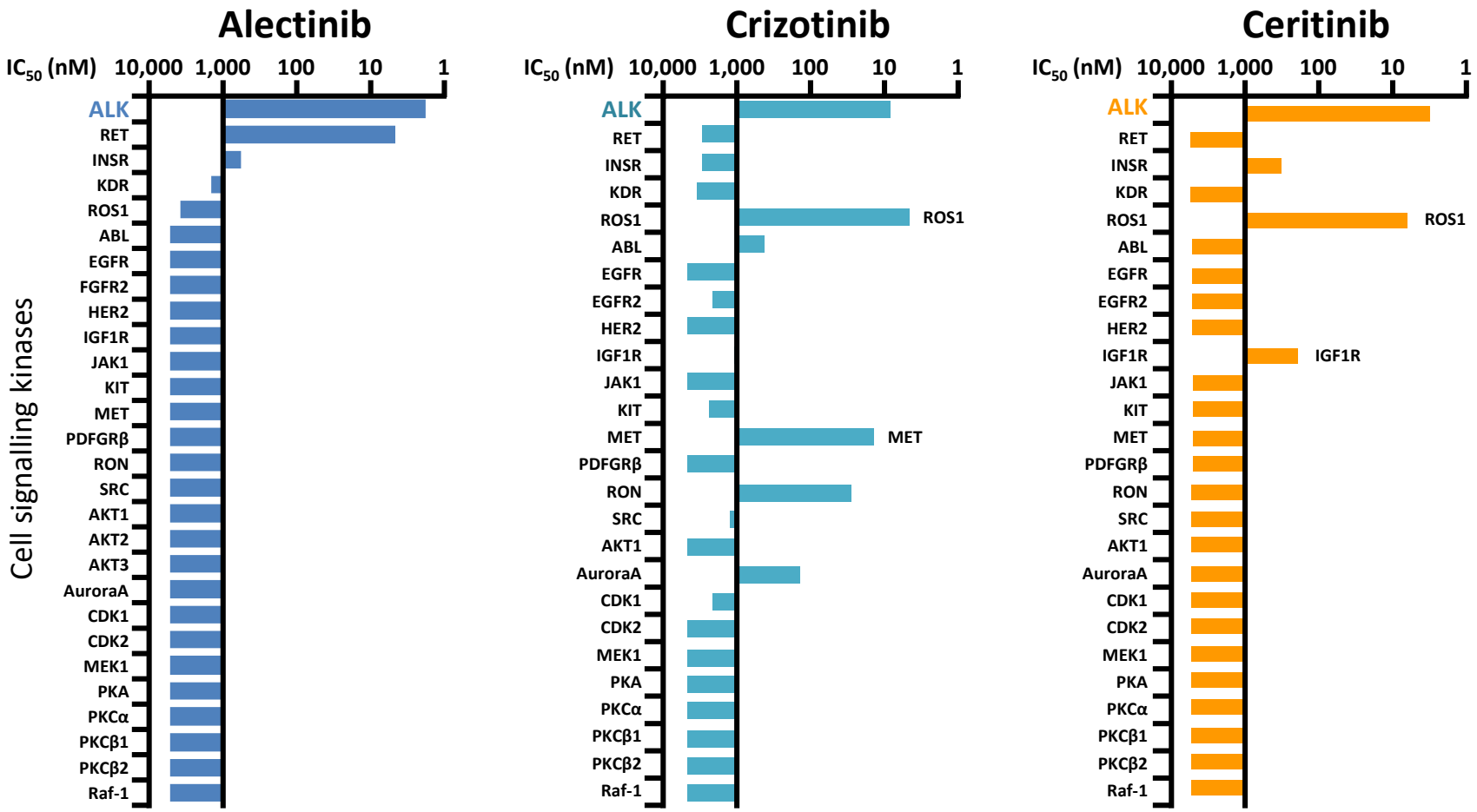


Novello et al. Ann Oncol 2016;27(Suppl. 5):v1

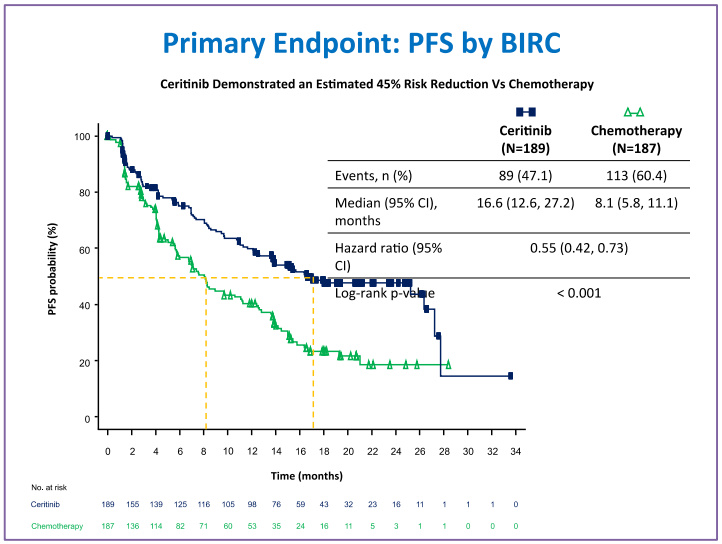
1st and 2nd Generation ALK inhibitors



Chugai, data on file;
Kinoshita, et al. Bioorg Med Chem 2012

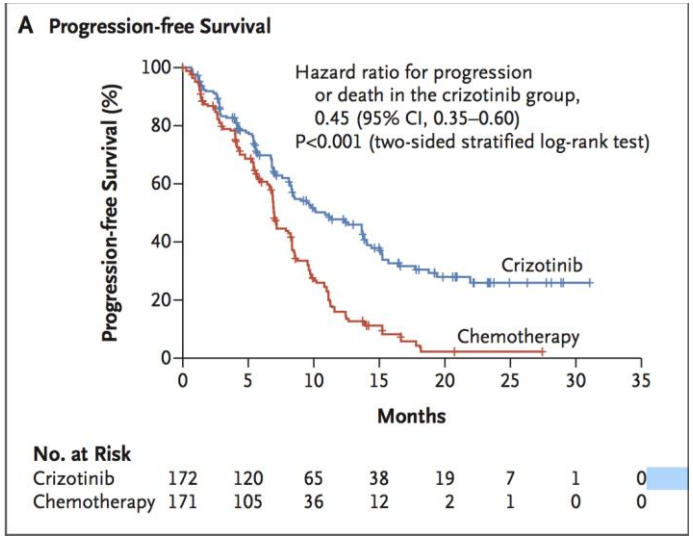
ASCEND-4

De Castro et al. WCLC 2016



PROFILE 1014

Solomon et al. NEJM 2014



ASCEND-4	PFS [95% CI]	HR (95%CI)	ORR
ceritinib	**16.6** (12.6,27.2)	**0.55**(0.42,0.73)	72.5%
chemoT	**8.1** (5.8,11.1)		26.7%

PROFILE	PFS [95% CI]	HR (95%CI)	ORR
crizotinib	**10.9** (8.3,13.9)	**0.45**(0.35,0.60)	74 %
chemoT	**7.0** (6.8,8.2)		45%

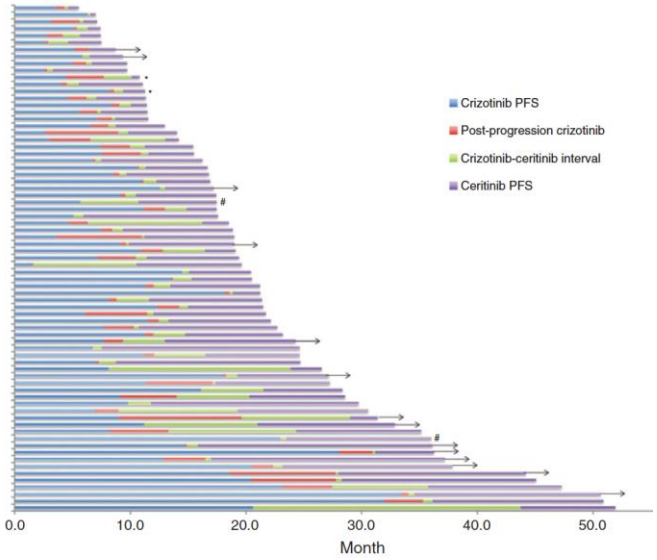
ALK+ NSCLC: Sequence is associated with prolonged survival

Cancer Therapy: Clinical

Clinical Cancer Research

Progression-Free and Overall Survival in ALK-Positive NSCLC Patients Treated with Sequential Crizotinib and Ceritinib

Justin F. Gainor[1], Daniel S.W. Tan[2], Tomasso De Pas[3], Benjamin J. Solomon[4], Aziah Ahmad[2], Chiara Lazzari[3], Filippo de Marinis[3], Gianluca Spitaleri[3], Katherine Schultz[1], Luc Friboulet[1], Beow Y. Yeap[1], Jeffrey A. Engelman[1], and Alice T. Shaw[1]

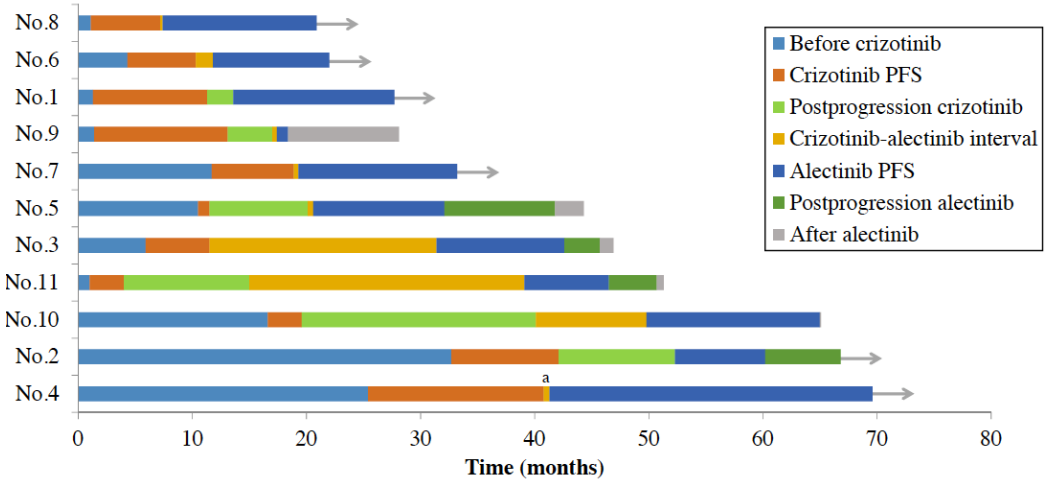


Median combined PFS: 17.4 months
Median OS: 49.4 months

Gainor et al. Clin Cancer Res 2015;21:2745

Progression-Free and Overall Survival of Patients With *ALK* Rearrangement–Positive Non–Small Cell Lung Cancer Treated Sequentially With Crizotinib and Alectinib

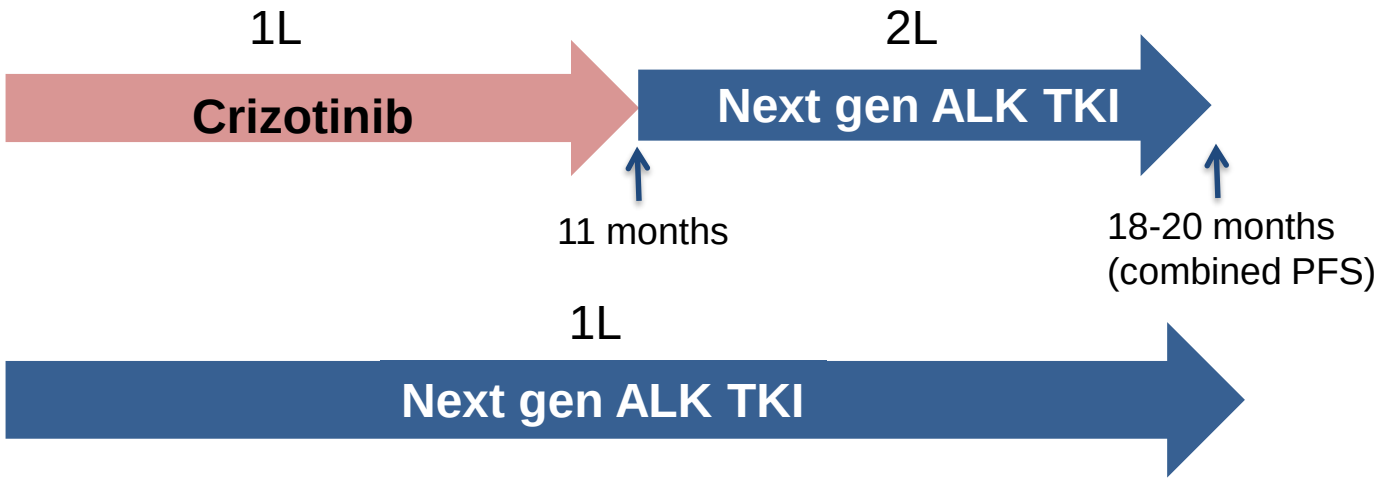
Satomi Watanabe,[1] Hidetoshi Hayashi,[1] Kunio Okamoto,[2] Kimiko Fujiwara,[3] Yoshikazu Hasegawa,[4] Hiroyasu Kaneda,[2] Kaoru Tanaka,[1] Masayuki Takeda,[1] Kazuhiko Nakagawa[1]



Median combined PFS: 18.2 months
Median OS: 51.1 months

Watanabe et al. Clin Lung Cancer 2016

What is Optimal First-line Tx for Advanced ALK+ NSCLC?



First-line Phase 3 studies of novel ALK TKIs in NSCLC

- **ALEX**: Alectinib vs Crizotinib
- **ASCEND 4**: Ceritinib vs Chemotherapy
- **ALTA**: Brigatinib vs. crizotinib
- **eXalt3**: Ensartinib vs. Crizotinib

The NEW ENGLAND JOURNAL of MEDICINE

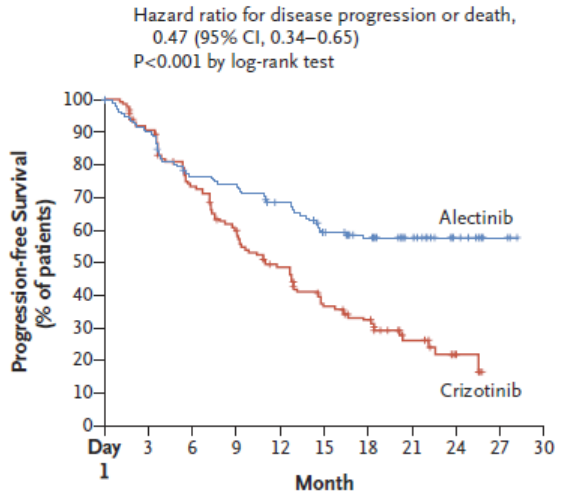
ORIGINAL ARTICLE

Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer

Solange Peters, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Shirish Gadgeel, M.D., Jin S. Ahn, M.D., Dong-Wan Kim, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Maurice Pérol, M.D., Rafal Dziadziuszko, M.D., Rafael Rosell, M.D., Ph.D., Ali Zeaiter, M.D., Emmanuel Mitry, M.D., Ph.D., Sophie Golding, M.Sc., Bogdana Balas, M.D., Johannes Noe, Ph.D., Peter N. Morcos, Pharm.D., and Tony Mok, M.D., for the ALEX Trial Investigators*

Median PFS not reached in the alectinib arm, with a lower confidence interval of 20.3 months, compared with a median PFS of 10.2 months in the crizotinib arm (HR, 0.34; *P* <.0001).

A Progression-free Survival

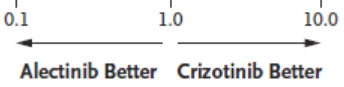


No. at Risk

Alectinib	152	135	113	109	97	81	67	35	15	3
Crizotinib	151	132	104	84	65	46	35	16	5	

B Subgroup Analysis

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	164/303	0.48 (0.35–0.66)
Age		
<65 yr	125/233	0.48 (0.34–0.70)
≥65 yr	39/70	0.45 (0.24–0.87)
Sex		
Female	91/171	0.39 (0.25–0.60)
Male	73/132	0.61 (0.38–0.98)
Race		
Asian	72/138	0.46 (0.28–0.75)
Non-Asian	92/165	0.49 (0.32–0.75)
Smoking status		
Active smoker	12/17	1.16 (0.35–3.90)
Nonsmoker	103/190	0.44 (0.29–0.66)
Former smoker	49/96	0.42 (0.23–0.77)
ECOG performance status		
0	44/97	0.40 (0.21–0.77)
1	105/186	0.48 (0.32–0.71)
2	15/20	0.74 (0.25–2.15)
CNS metastases at baseline		
Yes	78/122	0.40 (0.25–0.64)
No	86/181	0.51 (0.33–0.80)
Previous brain radiation		
Yes	26/47	0.33 (0.14–0.74)
No	138/256	0.52 (0.36–0.73)



Online First on June 6, 2017

2017 ASCO ANNUAL MEETING
Making a Difference in Cancer Care WITH YOU

ASCO DAILY NEWS

LUNG CANCER

ALEX Phase III Trial Suggests Alectinib Should Be First-Line Treatment for Patients With *ALK*-Positive Lung Cancer

JUNE 13, 2017

The results of ALEX, a global phase III trial, suggest that alectinib, an anaplastic lymphoma kinase (ALK) tyrosine-kinase inhibitor (TKI), leads to greater progression-free survival (PFS) and longer duration until central nervous system (CNS) progression in patients with untreated, advanced *ALK*-positive non–small cell lung cancer (NSCLC) compared with crizotinib, which is currently the first-line treatment for this disease.

"Our results establish alectinib as a new standard of care for patients with previously untreated, advanced *ALK*-positive lung cancer," Alice Tsang Shaw, MD, PhD, of the Massachusetts General Hospital, said. Dr. Shaw presented the findings in an Oral Abstract Session (**Abstract LBA9008**) on June 6.

According to Dr. Shaw, alectinib is already standard therapy for patients with *ALK*-positive NSCLC who were previously treated with crizotinib because alectinib demonstrates robust clinical activity in patients with crizotinib resistance.

The trial enrolled 303 treatment-naive patients from 29 countries. Patients were randomly assigned to receive crizotinib or alectinib, a next-generation ALK TKI that is structurally distinct from crizotinib but, unlike crizotinib, is CNS penetrant.[1] Approximately 40% of the patients in each treatment arm had asymptomatic CNS metastases; among those, approximately 40% had received treatment, such as whole-brain radiation therapy, for CNS metastases.

Category
- Any -
Topic
- Any -

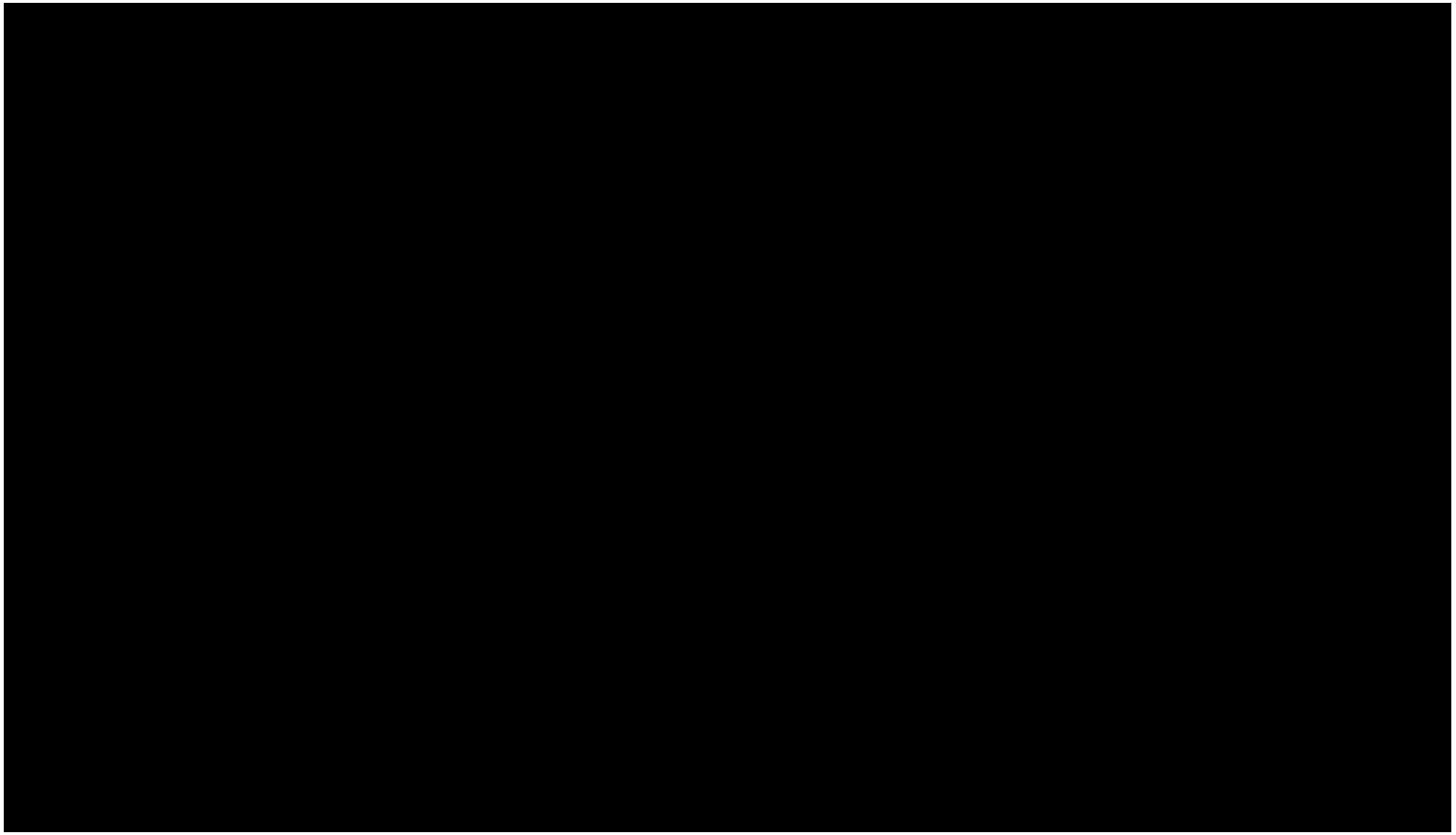
Follow-Up of RESONATE Trial Supports Survival Benefits of Ibrutinib for Previously Treated CLL

Subgroup Analysis of CheckMate 141 Supports Nivolumab for Platinum-Refractory Head and Neck Cancer

ALEX Phase III Trial Suggests Alectinib Should Be First-Line Treatment for Patients With *ALK*-Positive Lung Cancer

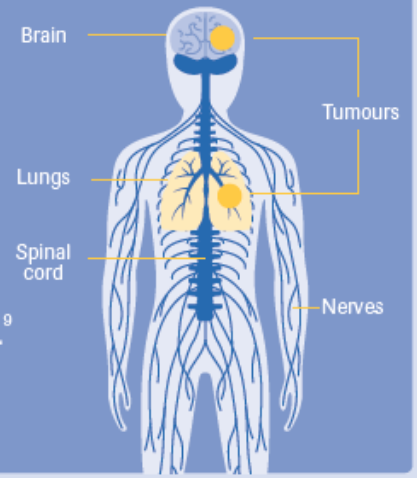
SIRT Offers No Benefit When Added to Chemotherapy for mCRC With Liver Metastases

Save the Best for Last

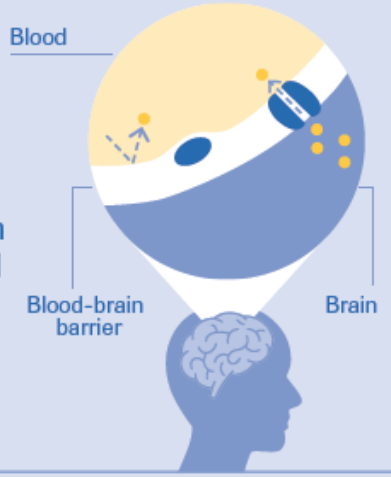


CNS metastases

The central nervous system **(CNS) is a common site of progression.**[9]



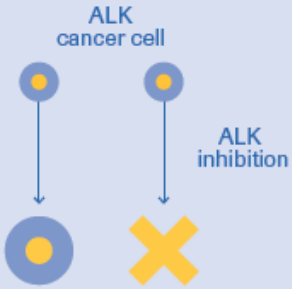
CNS metastases are difficult to treat as the blood-brain barrier blocks and actively removes some drug molecules from the brain.[10]



First-line treatments[11]

Surgery | Chemotherapy | Targeted therapies

ALK inhibitors stop the ALK mutated protein from working, and **inhibit the growth and survival of the ALK+ cancer cell.**[5,6]



Most patients progress on the current standard of care within one year of treatment, and approximately **60% will develop CNS metastases.**[12,13]

A treatment which is active in the CNS can delay **development and worsening** of CNS metastases.[5]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer

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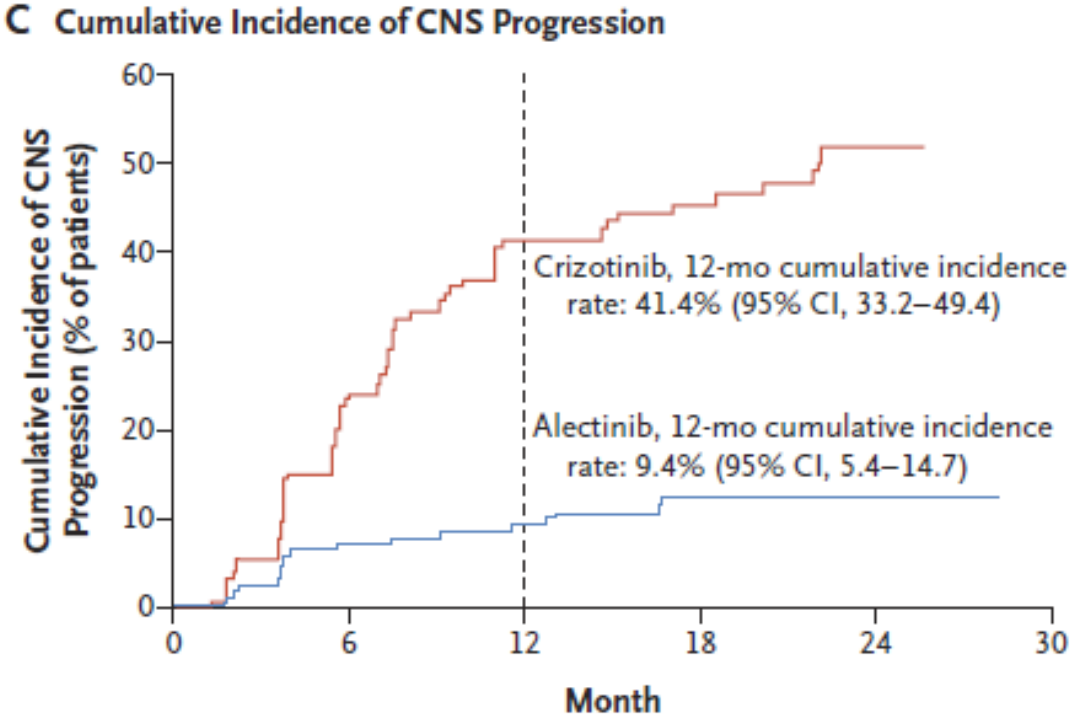
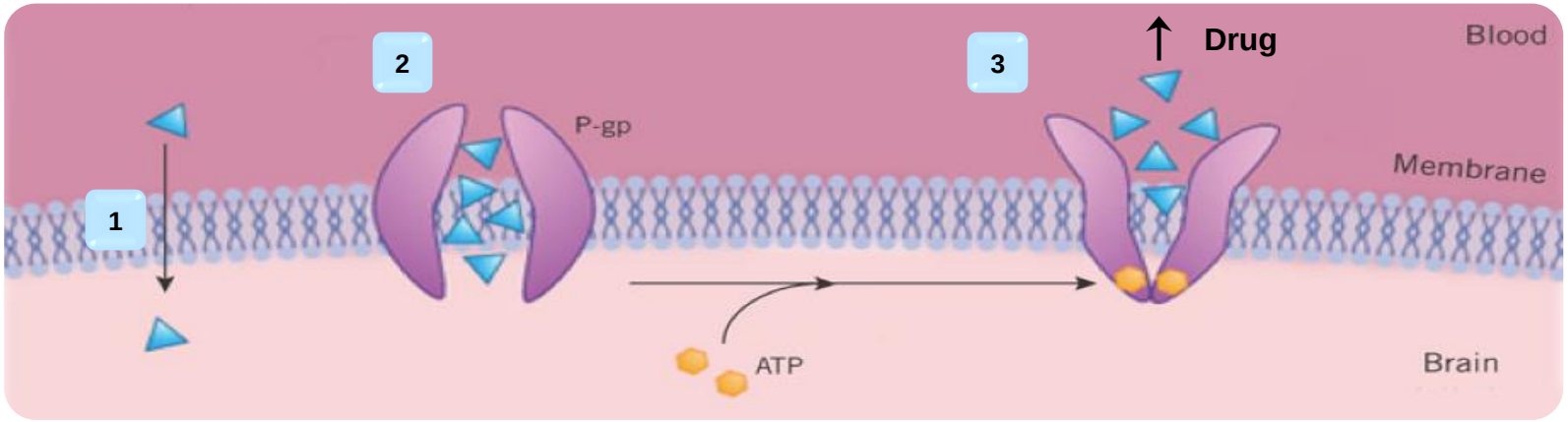


Online First on June 6, 2017

Alectinib is not transported out of the brain

The brain is protected by the BBB, a network of tightly connected cells

1. Drugs enter the brain by crossing the BBB
2. The drug-efflux-transporter protein P-gp is expressed at high levels in the brain[1,2]
3. P-gp actively exports drugs back across the BBB into the bloodstream in an ATP-dependent manner[2,3]



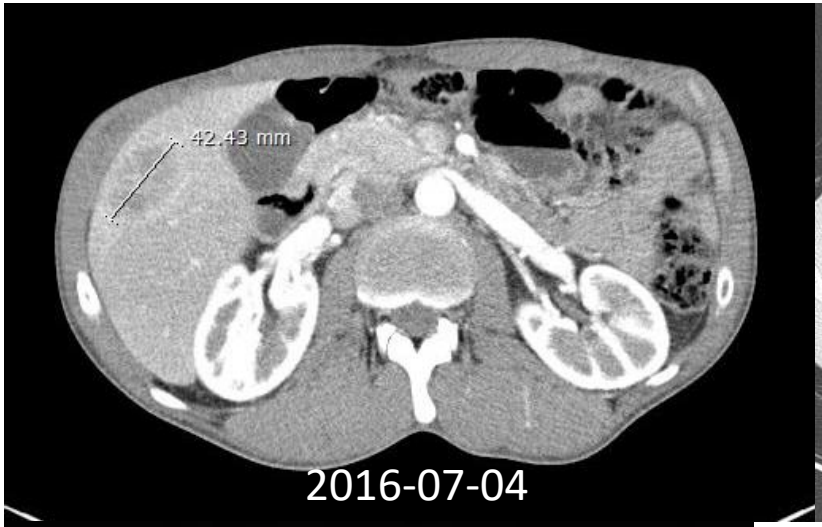
Preclinical data show that alectinib is not a substrate for the drug efflux transporter P-gp[3], and is therefore not actively transported out of the brain

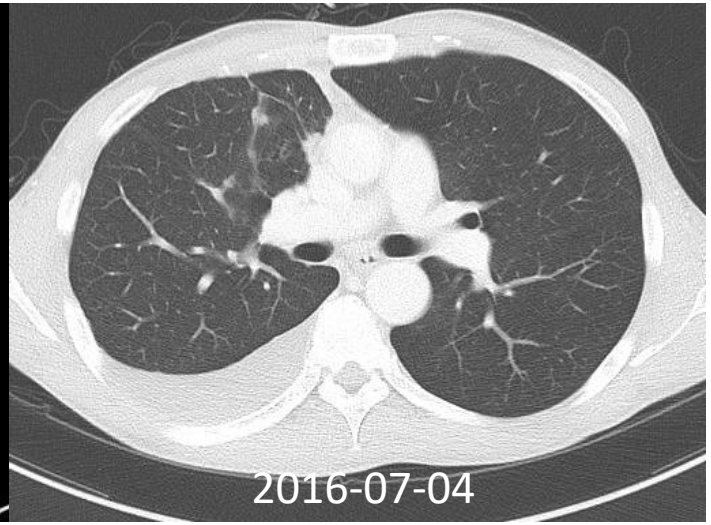
ATP = adenosine triphosphate
BBB = blood-brain barrier; P-gp = P-glycoprotein

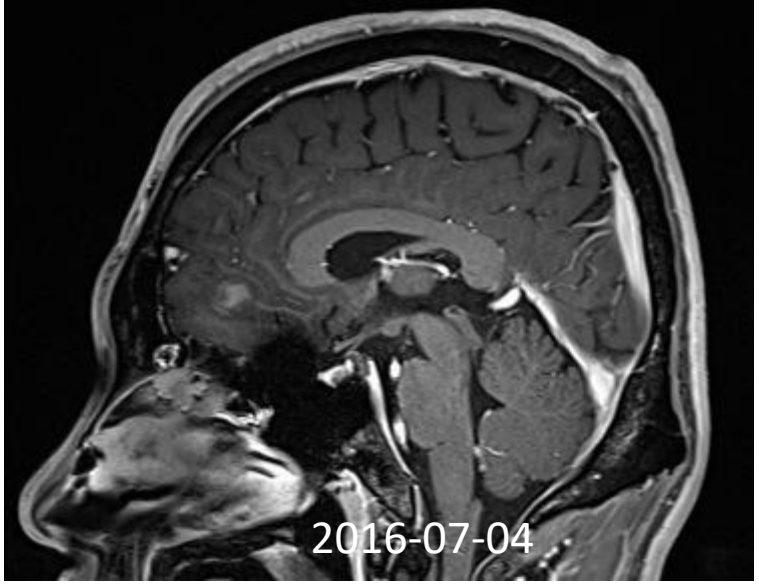
1. Thiebaut, et al. Proc Natl Acad Sci 1987; 2. Misra, et al. J Pharm Pharmaceut Sci 2003
3. Kodama, et al. Cancer Chemother Pharmacol 2014

43/M, ADC IV(T3N3M1a)

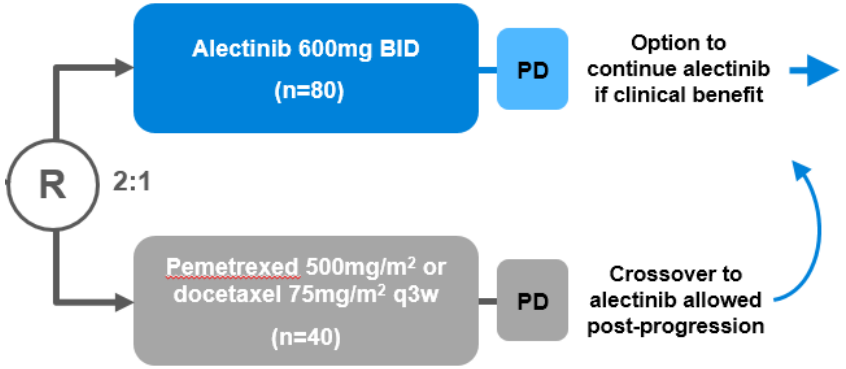
- 1AP4: 2013.9.12 ~ *maintenance A5-22 : 2013.12.16 ~ 2015.4.6
- 2Xalkori: 2015.5.15 ~ 2016.5.18





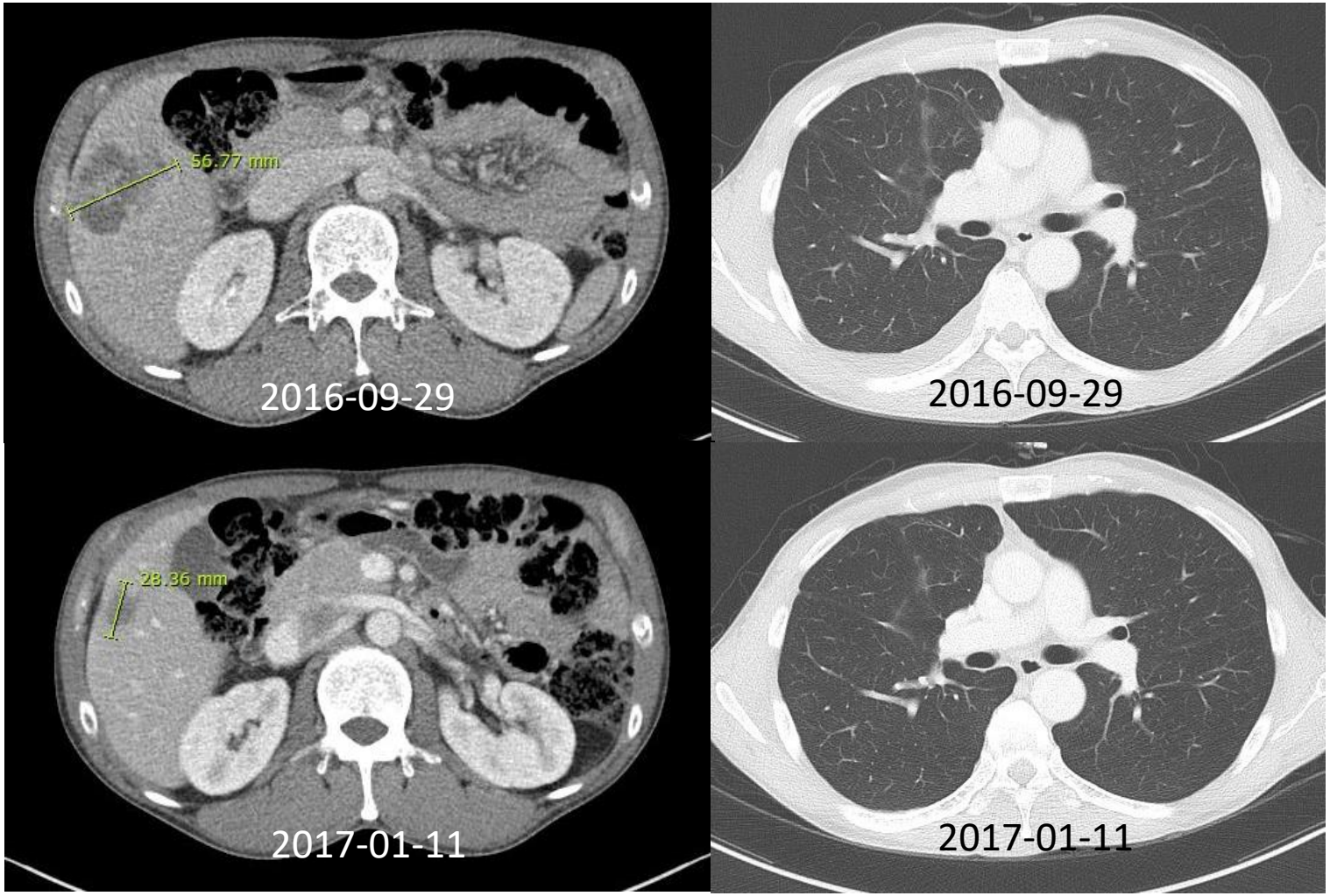


MO29750: phase III trial of alectinib versus chemotherapy in previously treated *ALK*+ NSCLC



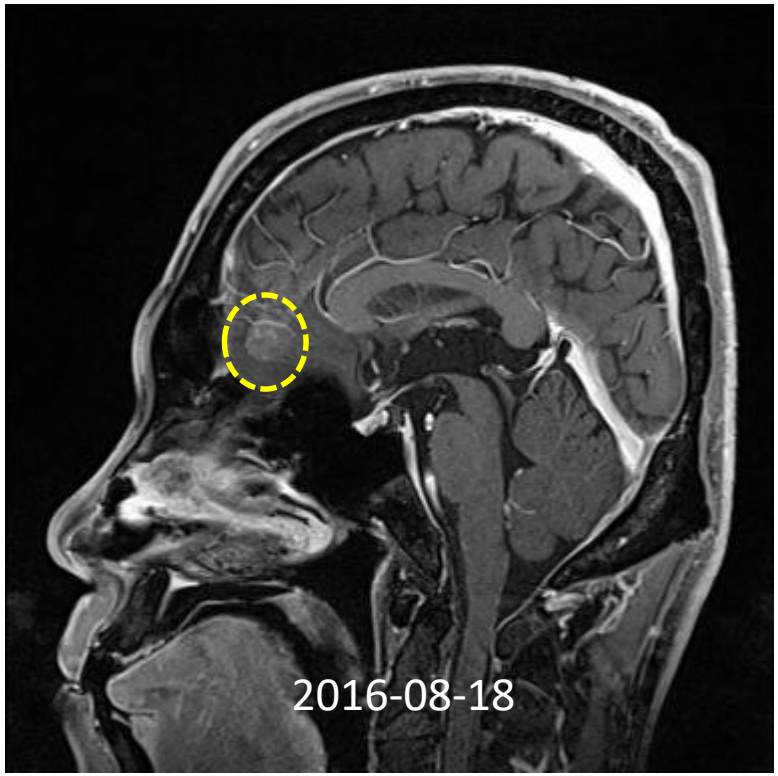
44/M, ADC IV(T3N3M1a)

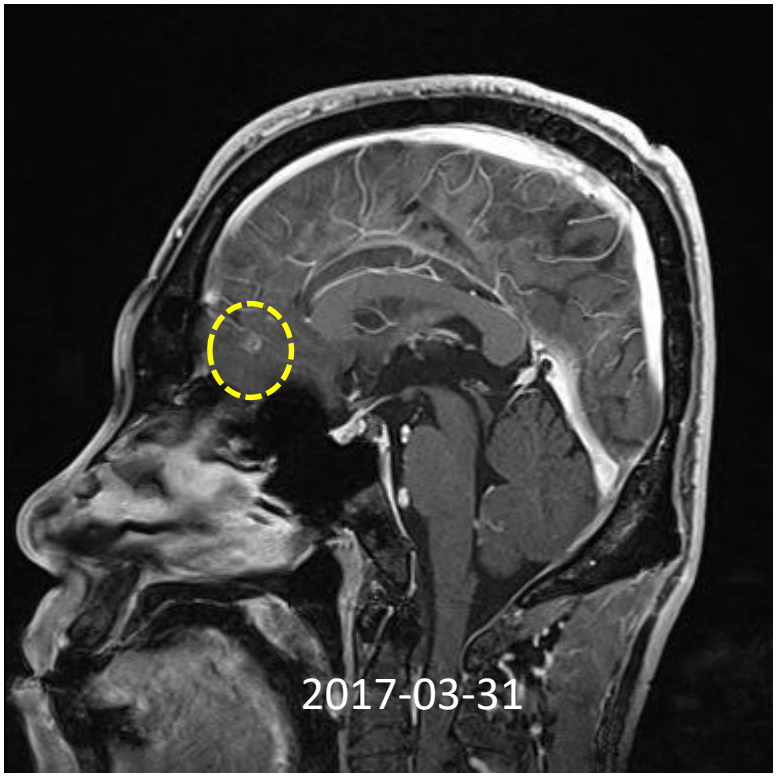
- 1AP4: 2013.9.12 ~ *maintenance A5-22 : 2013.12.16 ~ 2015.4.6
- 2Xalkori: 2015.5.15 ~ 2016.5.18
- 3MO29750(D4): 2016.7.11 ~ 9.12
  Alectinib: 2016.10.17 ~



44/M, ADC IV(T3N3M1a)

- 1AP4: 2013.9.12 ~ *maintenance A5-22 : 2013.12.16 ~ 2015.4.6
- 2Xalkori: 2015.5.15 ~ 2016.5.18
- 3MO29750(D4): 2016.7.11 ~ 9.12
  Alectinib: 2016.10.17 ~





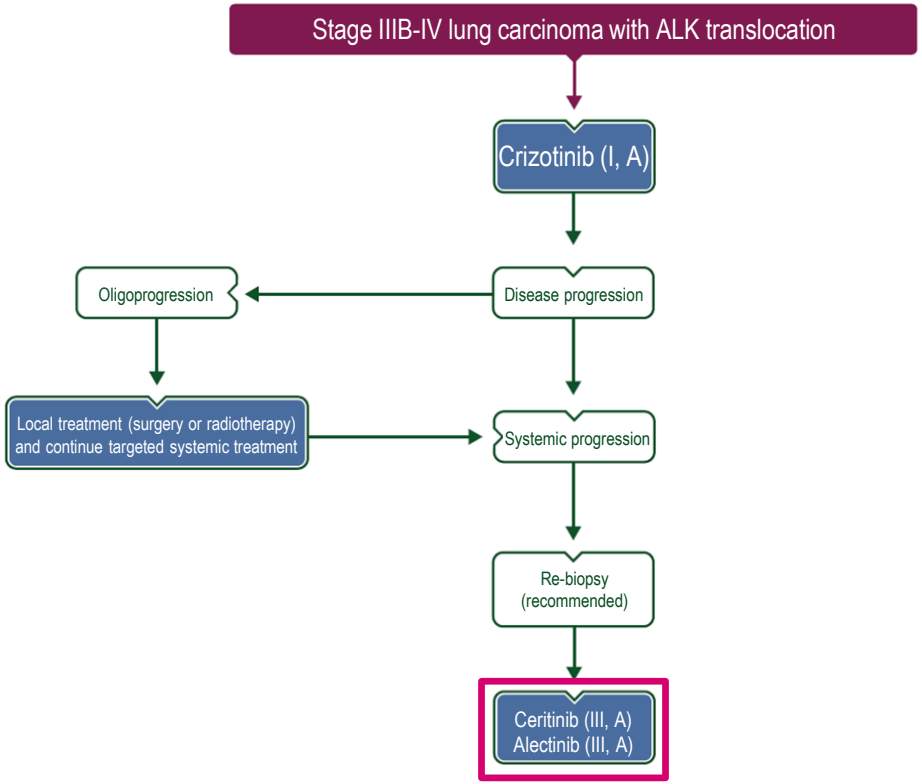
Crizotinib: Today our standard in first-line
Second generation TKIs at progression

clinical practice guidelines

Annals of Oncology 27 (Supplement 5): v1–v27, 2016
doi:10.1093/annonc/mdw326

Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

S. Novello[1], F. Barlesi[2], R. Califano[3,4], T. Cufer[5], S. Ekman[6], M. Giaj Levra[7], K. Kerr[8], S. Popat[9], M. Reck[10], S. Senan[11], G. V. Simo[12], J. Vansteenkiste[13] & S. Peters[14] on behalf of the ESMO Guidelines Committee*



Novello et al. Ann Oncol 2016;27(Suppl. 5):v1

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Non-Small Cell Lung Cancer

Version 2.2017 — October 26, 2016

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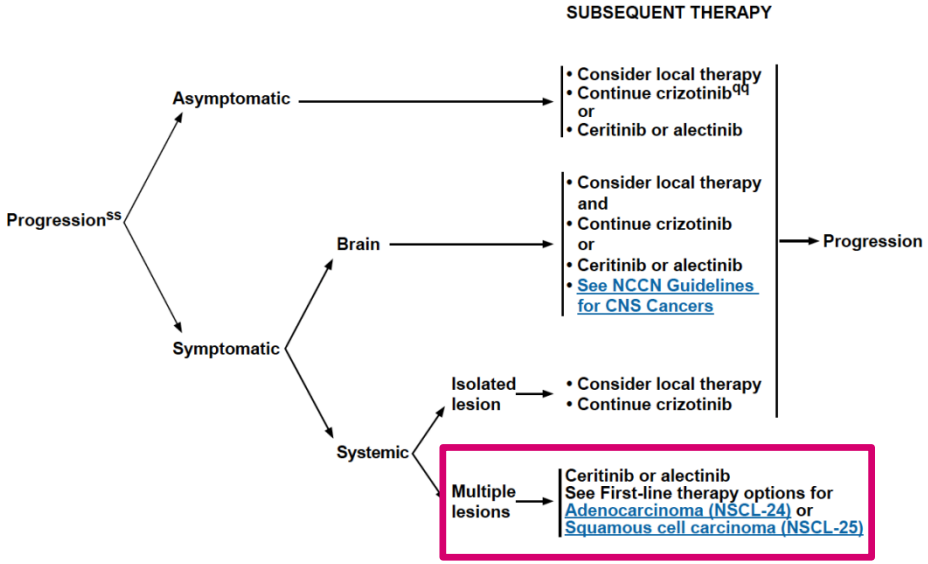
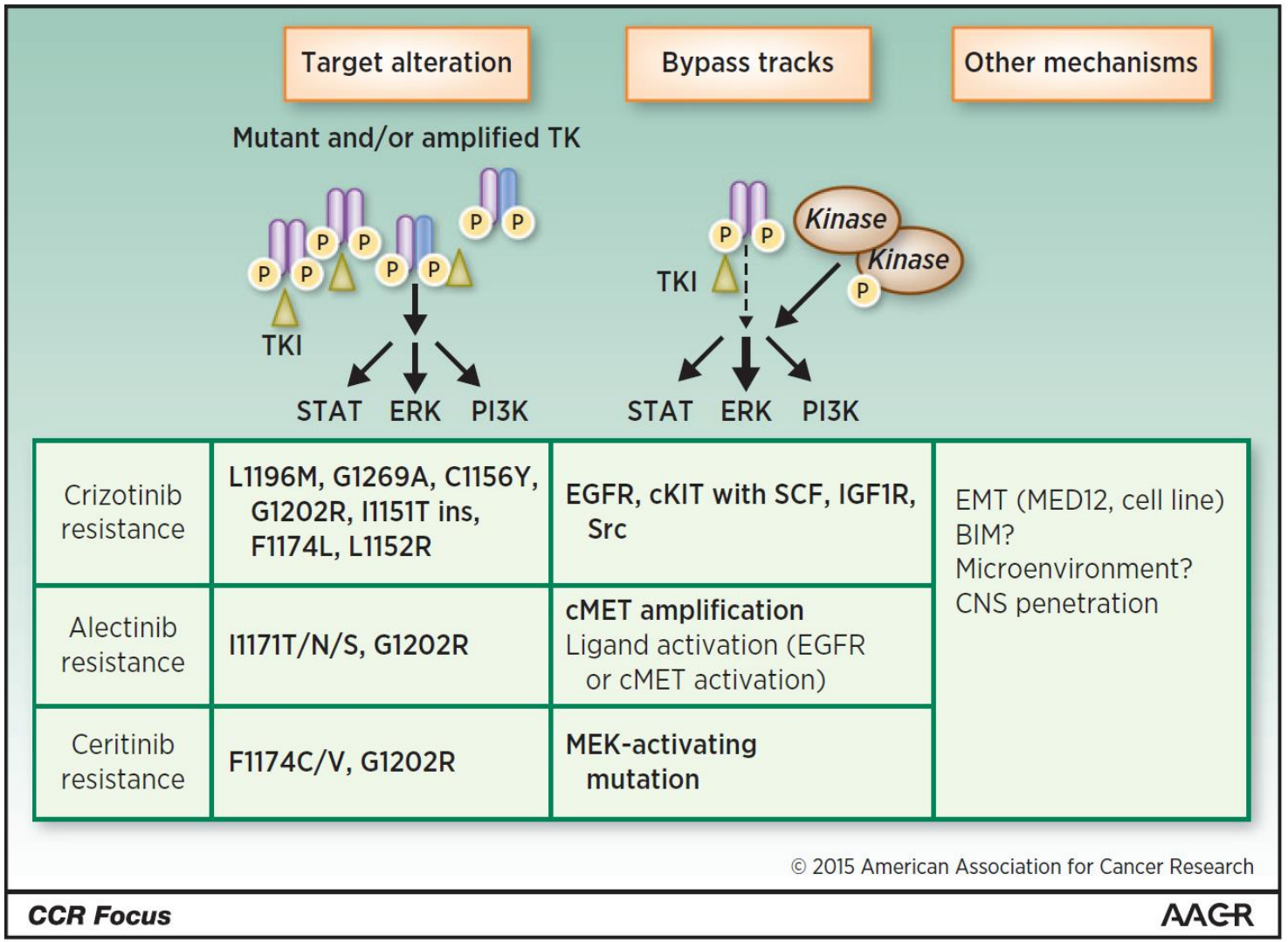


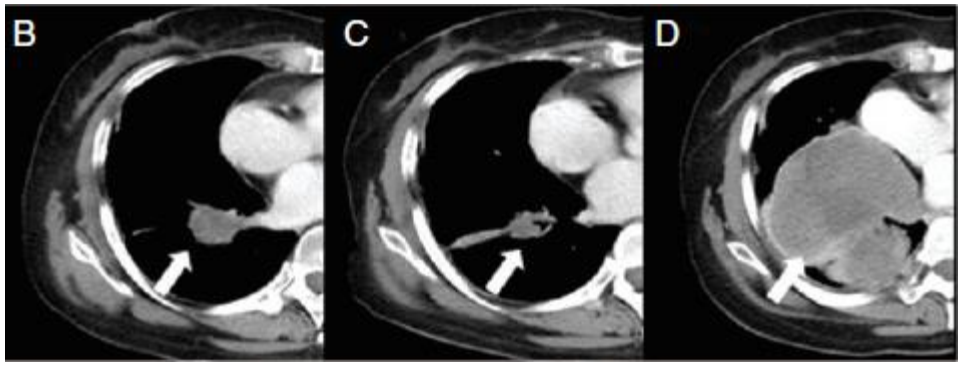
Mechanism of Acquired Resistance to ALK Inhibitors



Crizotinib resistance	L1196M, G1269A, C1156Y, G1202R, I1151T ins, F1174L, L1152R	EGFR, cKIT with SCF, IGF1R, Src	EMT (MED12, cell line) BIM? Microenvironment? CNS penetration
Alectinib resistance	I1171T/N/S, G1202R	cMET amplification Ligand activation (EGFR or cMET activation)	
Ceritinib resistance	F1174C/V, G1202R	MEK-activating mutation	

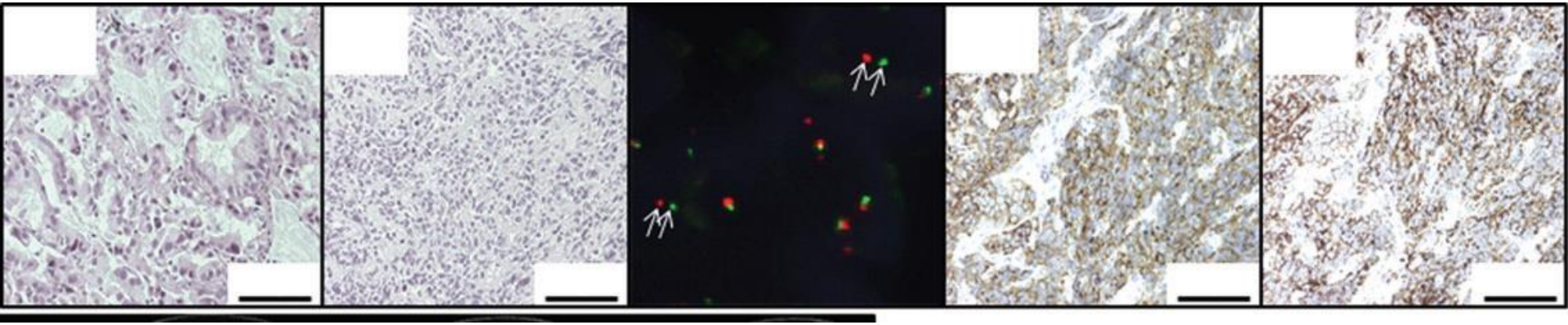
Katayama R et al. Clin Cancer Res 2015;21(10):2227-2235

Small cell transformation as resistance to Alectinib



Before Alectinib

After Alectinib

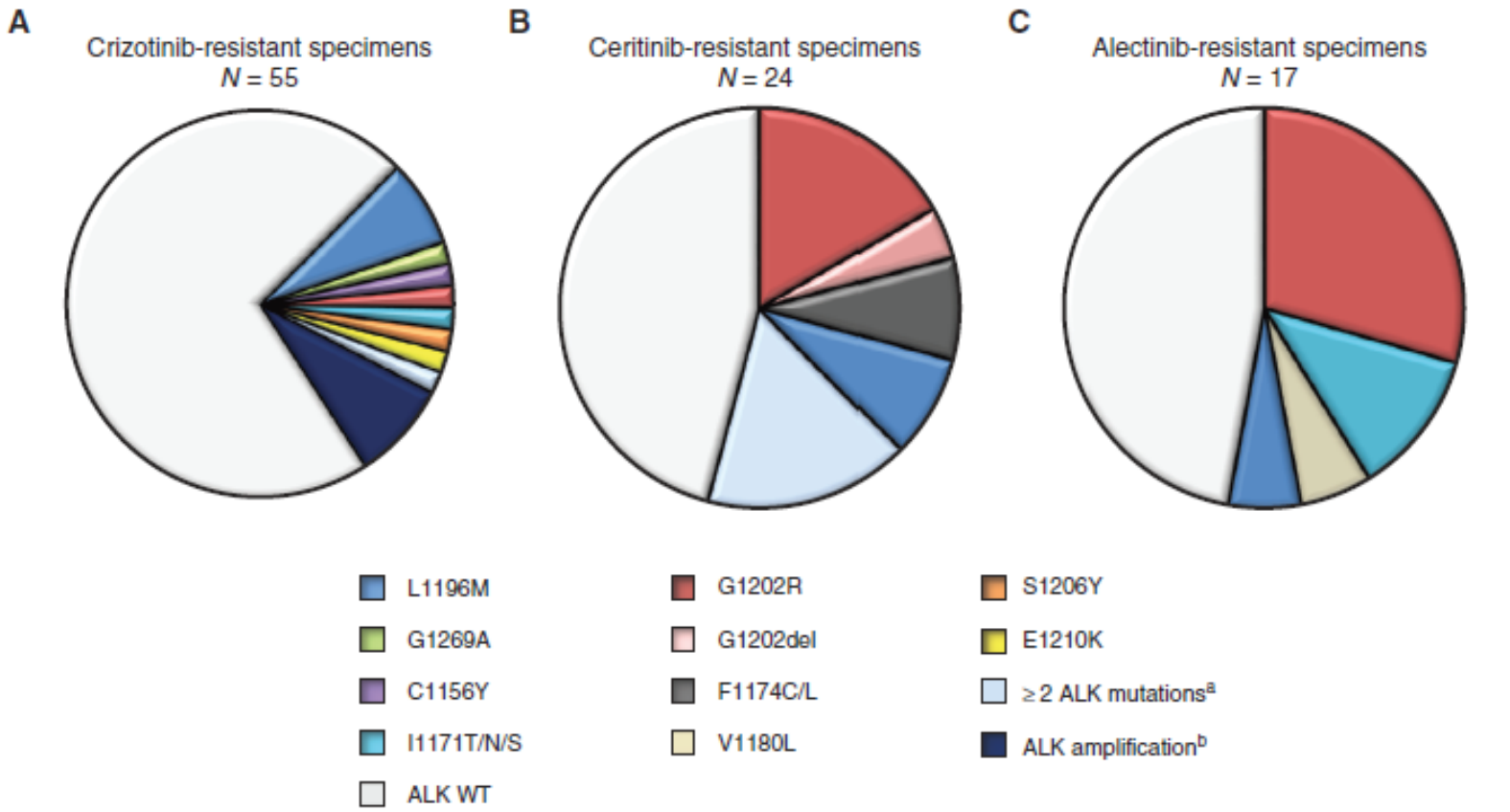


Synaptophysin

CD56

Takegawa et al, Ann Oncol 2016

Overview of on-target mechanisms of resistance



Cancer Discov 2016;6(10):1118-1133

Lorlatinib potently inhibits ALK resistance mutations

Cellular ALK phosphorylation mean IC_{50} (nmol/L)

Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4–ALK V1	38.6	4.9	11.4	10.7	2.3
EML4–ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4–ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4–ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4–ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4–ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4–ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4–ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4–ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4–ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4–ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4–ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4–ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4–ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4–ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

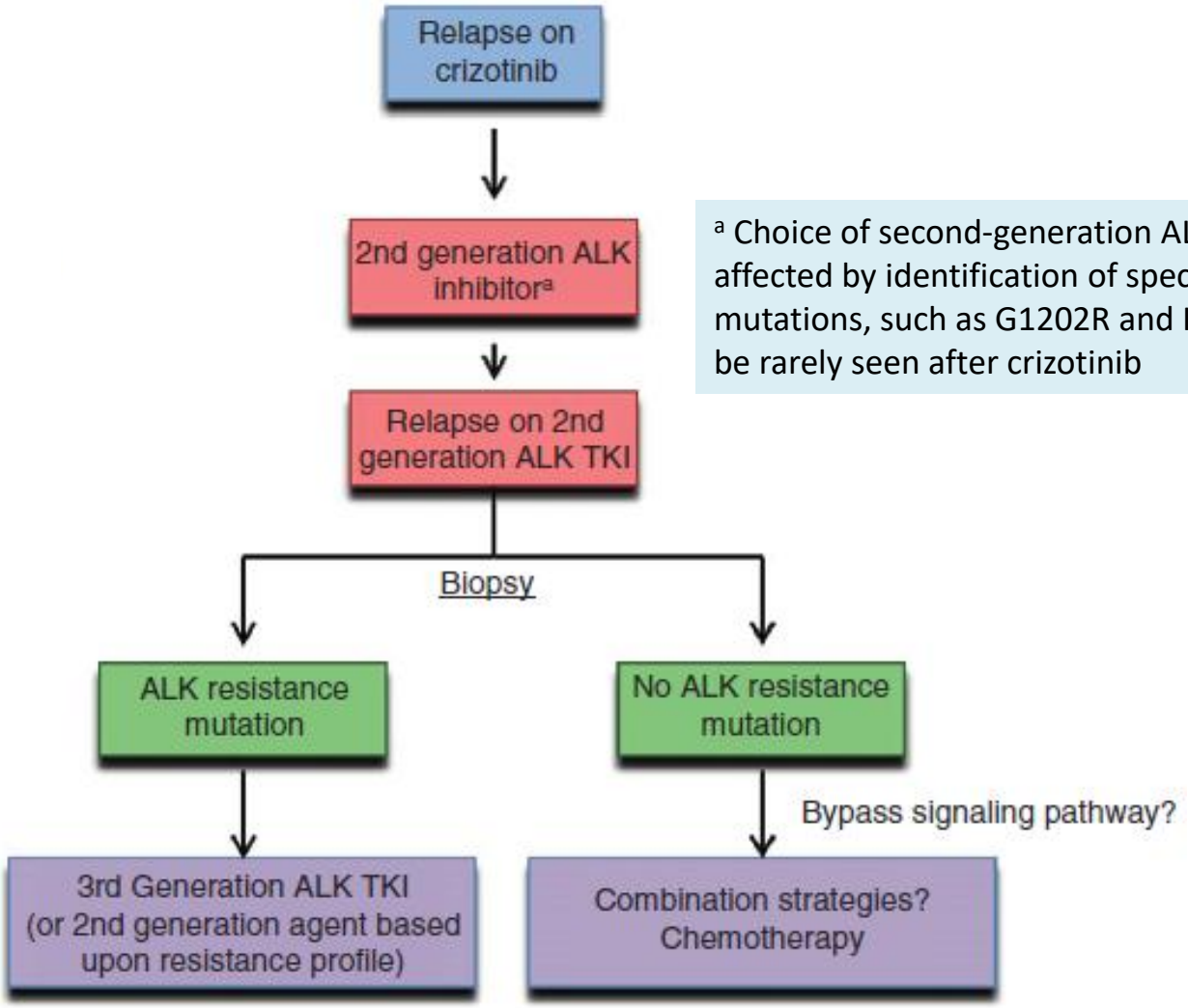
$IC_{50} \leq 50$ nmol/L

$IC_{50} > 50 < 200$ nmol/L

$IC_{50} \geq 200$ nmol/L

Cancer Discov 2016;6(10):1118-1133

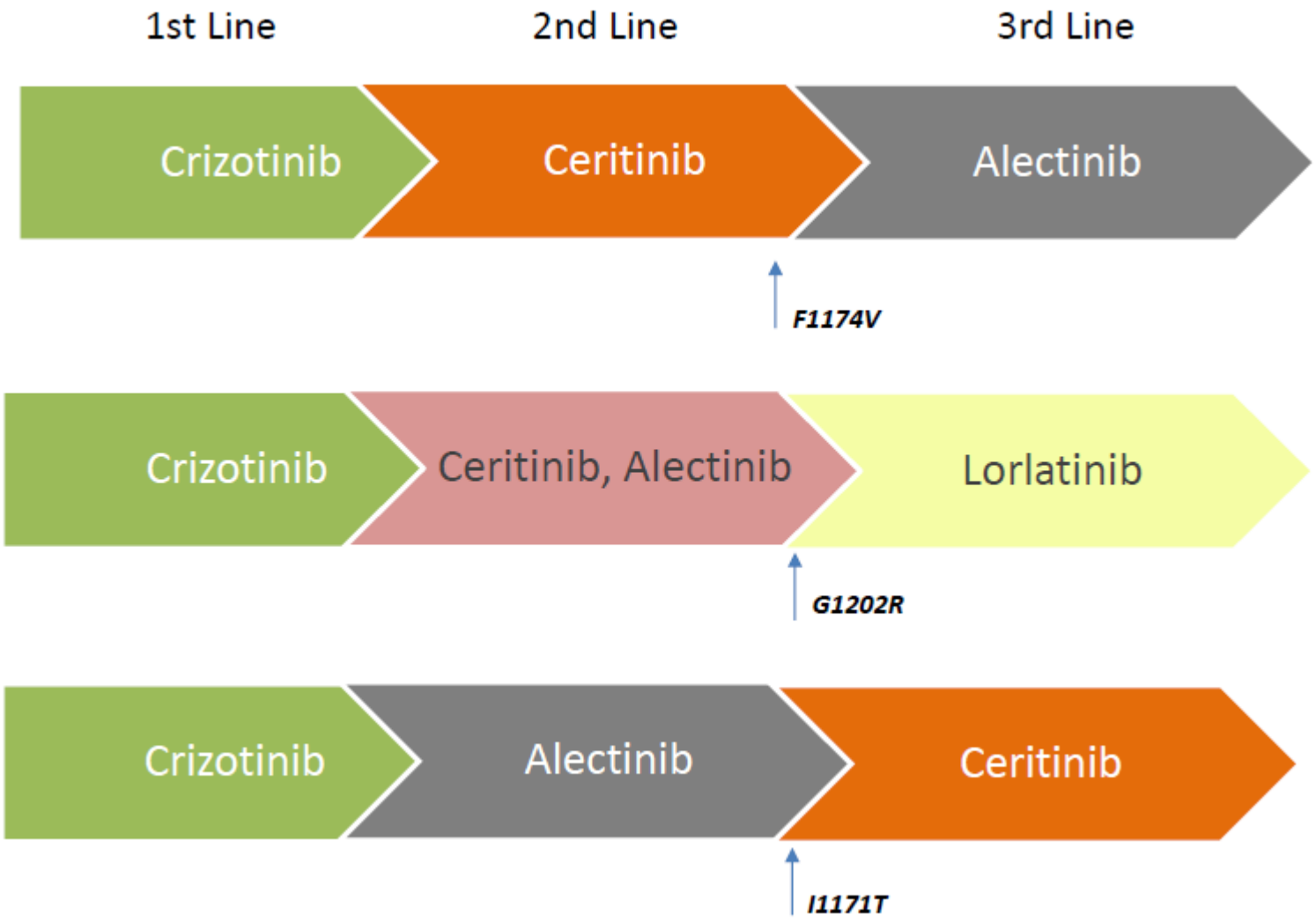
Proposed schema for the clinical approach to ALK(+) patients with acquired resistance



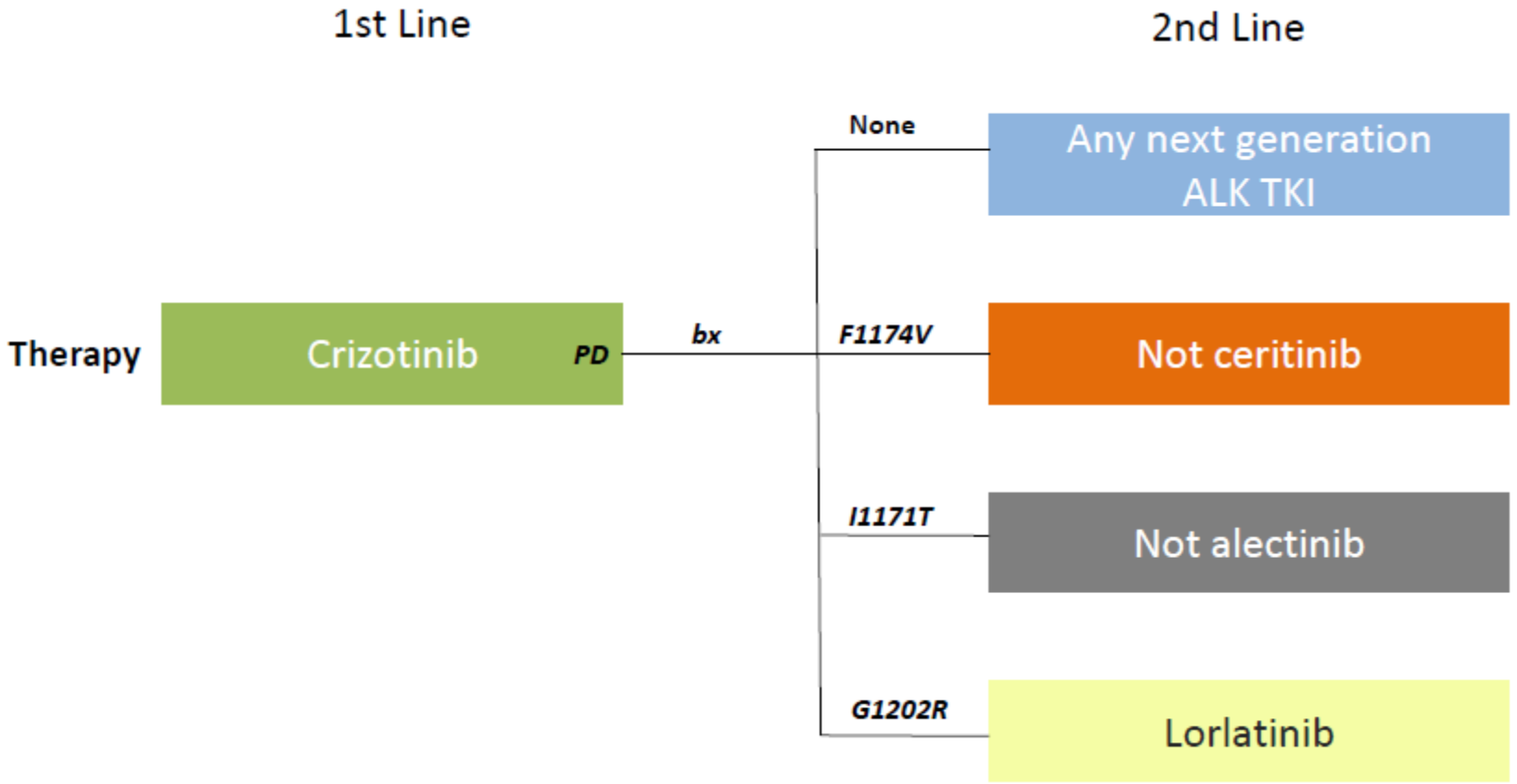
[a] Choice of second-generation ALK inhibitors may be affected by identification of specific *ALK* resistance mutations, such as G1202R and I1171N/S/T, which can be rarely seen after crizotinib

Cancer Discov 2016;6(10):1118-1133

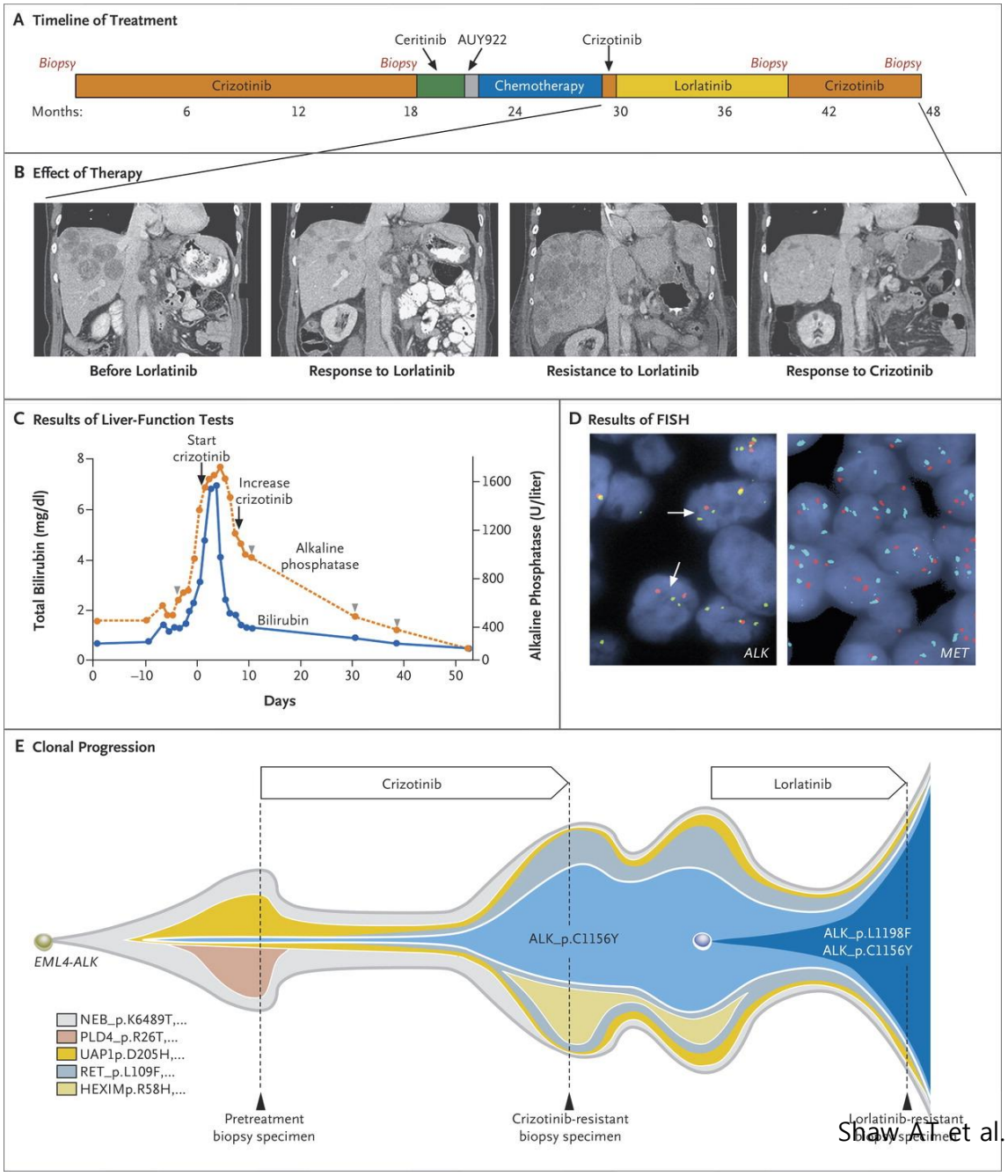
Possible Sequential Treatment According to Mutational Status



Tailoring selection of ALK inhibitors based on Mutational Status



Acquired Resistance to Lorlatinib and Resensitization to Crizotinib

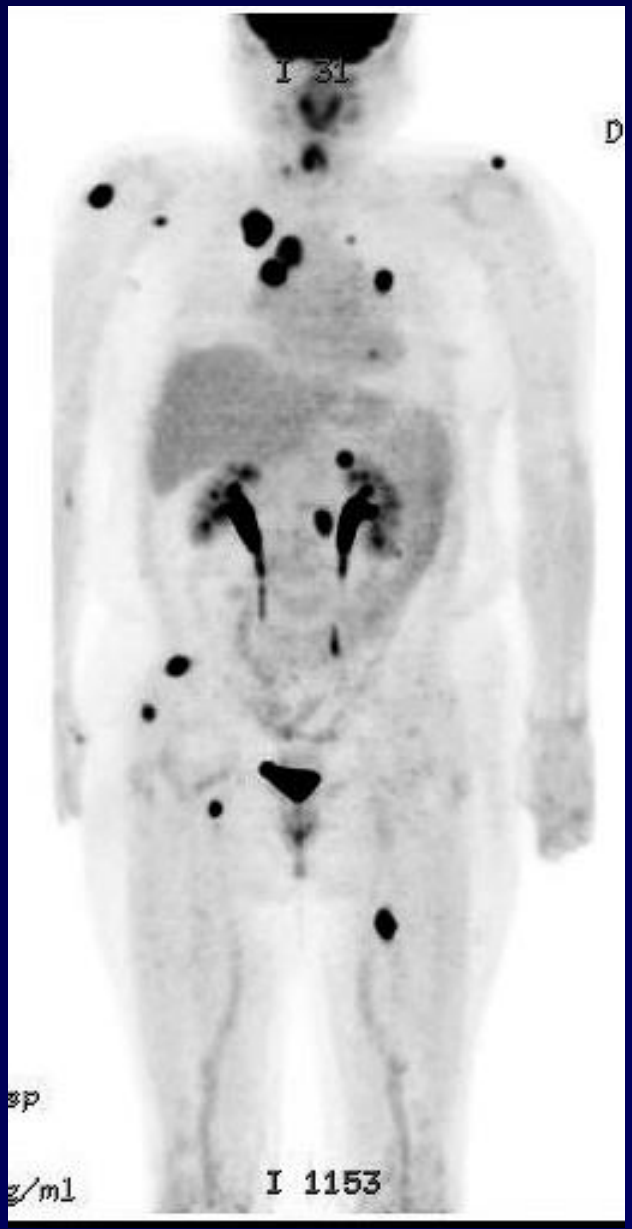


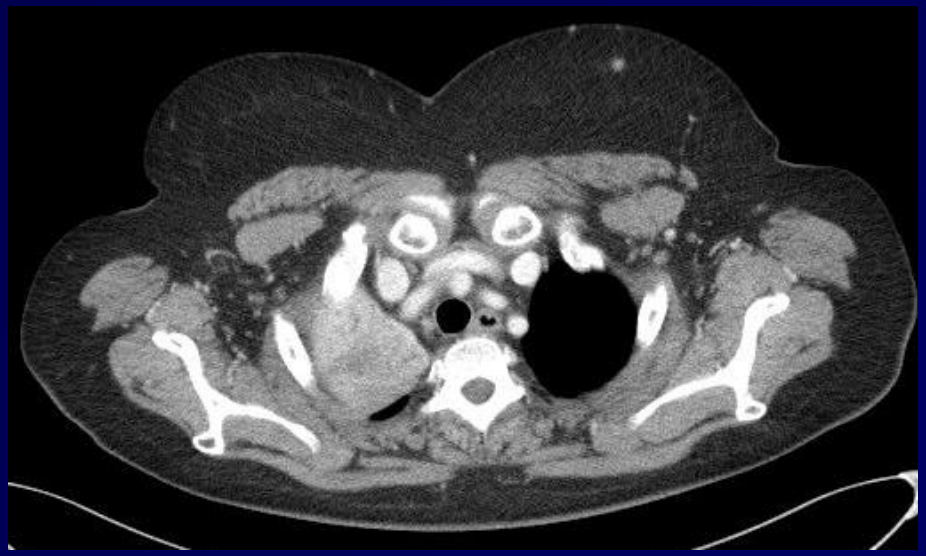
Shaw AT et al. N Engl J Med 2016;374:54-61

Q3. ALK 표적치료 동안 모니터링 해야 할 것은?

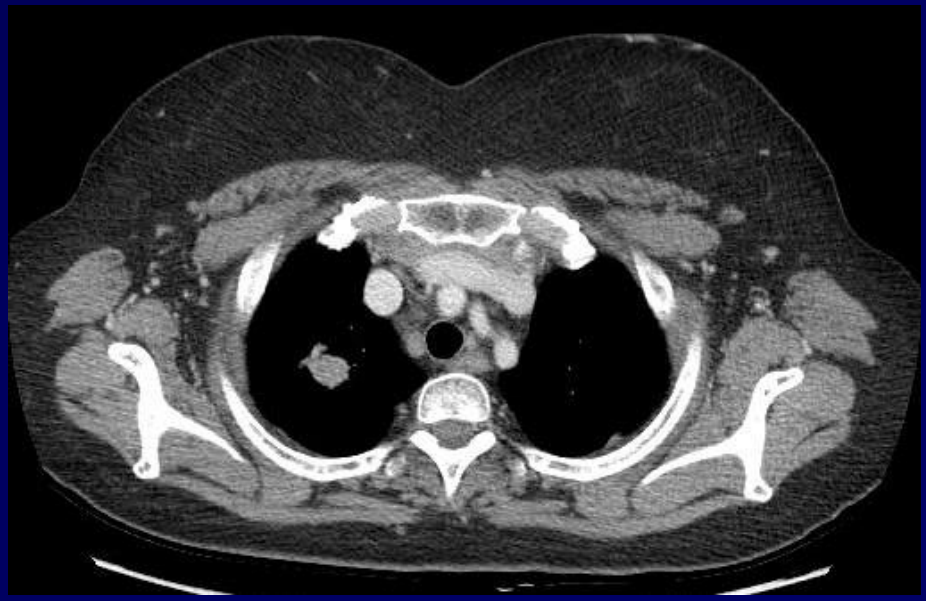
1) 심전도
2) 간기능검사
3) 폐기능검사
4) 흉부 X선 검사
5) 상기 검사 모두

56/F SQC, T2a, N3, M1b, wEGFR, ALK FISH +





Crizotinib since Apr 14 ~ May 13 2015



56/F SQC, T2a, N3, M1b, wEGFR, ALK FISH +

Crizotinib since Apr 14 2015 ~ May 13 2015

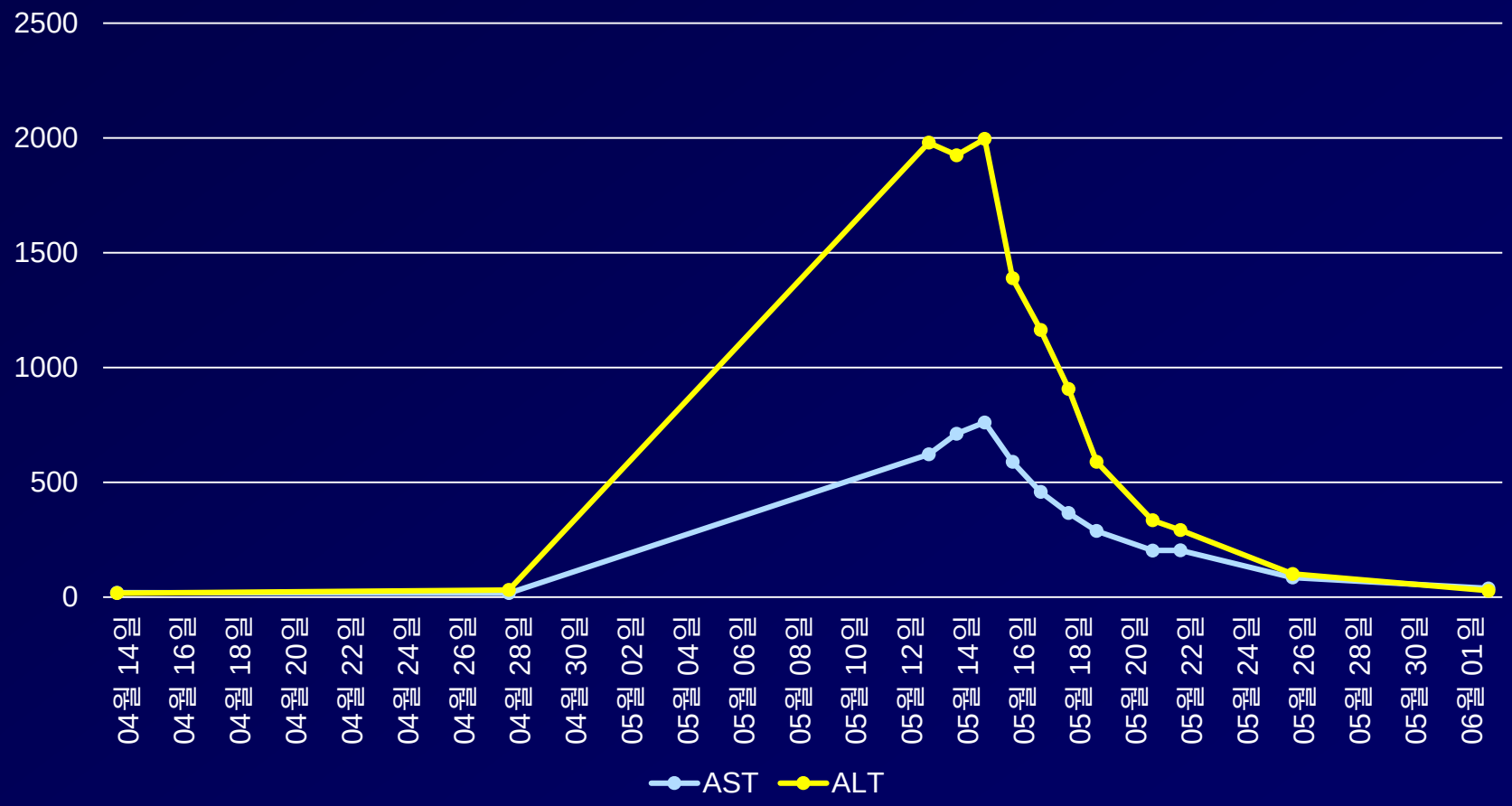


Table 1: Summary of Incidence of Common Treatment-related Adverse Events in Clinical Trials of Approved ALK Inhibitors, Including Grade 3–4

Adverse Event	Crizotinib (n=172)		Ceritinib (n=255)		Alectinib (n=122)	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Diarrhoea	43	0	86	6	5	0
Constipation	27	<1	29	0	15	0
Nausea	53	0	80	4	6	0
Vomiting	40	0	60	4		
Abdominal pain	8	0	54	2		
Oesophageal disorder*	11	0	16	1		
Fatigue	20	2	52	5	14	1
Oedema	28	0			9	1
Myalgia					17	1
Vision disorder	62	0				
Rash	10	0	16	0	9	0
Upper respiratory infection	2	0				
Dizziness	16	0				
Dyseugia	12	0			20	0

**Oesophageal disorder: dyspepsia, gastroesophageal reflux disease, dysphagia. ALK = anaplastic lymphoma kinase. Data sources: Pfizer,[11] Novartis,[27] Ou et al., 2015.[30]*

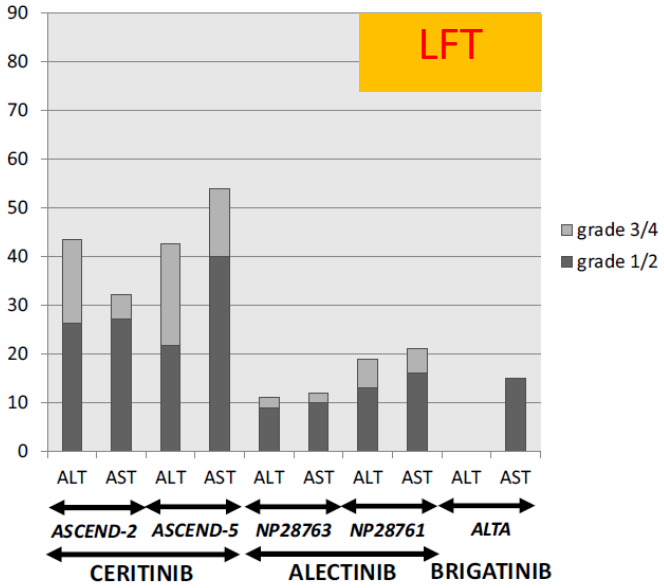
Table 2: Key Laboratory Abnormalities Associated with Approved ALK Inhibitors, Including Grade 3–4

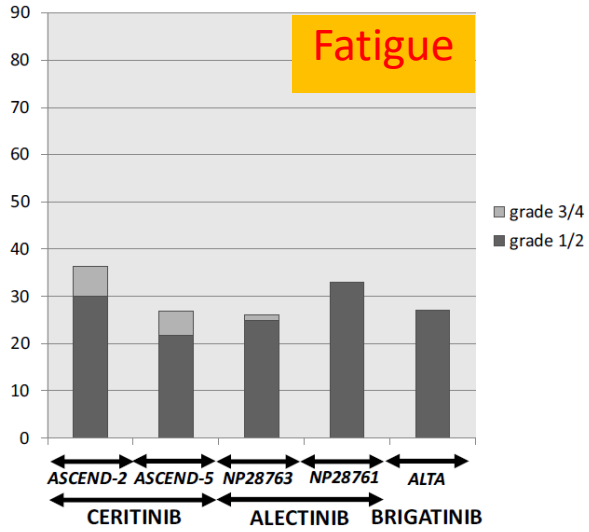
	Crizotinib (n=172)		Ceritinib (n=255)		Alectinib (n=58)	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Haemoglobin decreased			84	5		
ALT increase	13	5	80	27	9	2
AST increase	9	2	75	13	10	2
Elevated aminotransferase						
Creatinine increase			58	2		
γ-glutamyl transpeptidase						
Glucose increase			49	13		
Reduced neutrophils						
Phosphate decrease			36	7		
Bilirubin increase			15	1	8	1
Lipase increase			28	10		

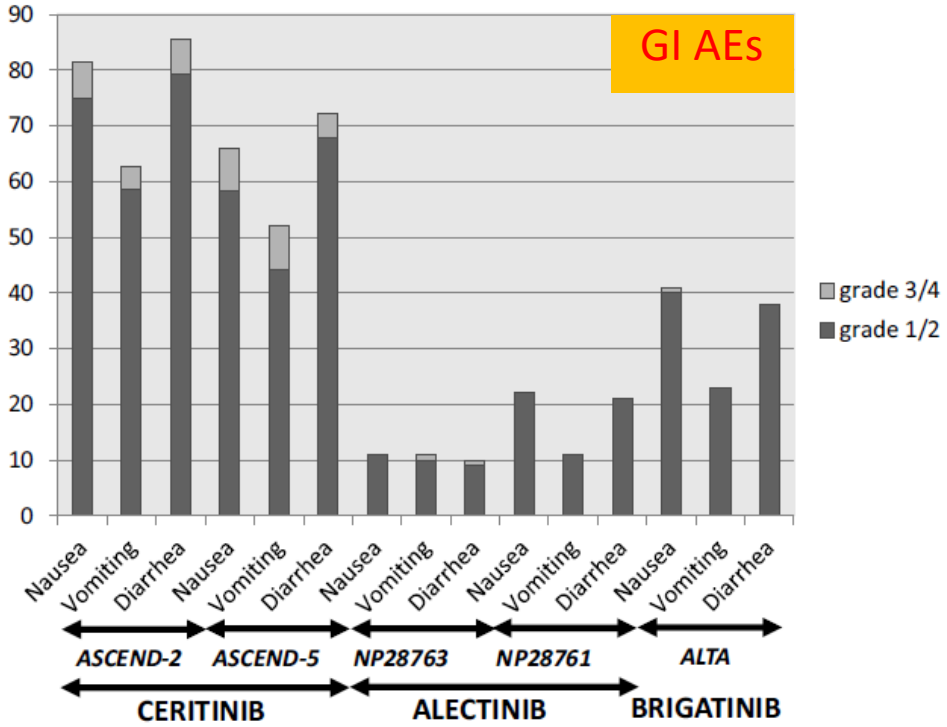
ALK = anaplastic lymphoma kinase; AST = aspartate aminotransferase; ALT = alanine aminotransferase. Data sources: Pfizer,[11] Novartis,[27] Ou et al., 2015.[30]

Rolfo C, et al. *Eur Oncol Haematol.* 2015;11(2):1-6.

Safety profiles of 2nd generation ALK-TKIs





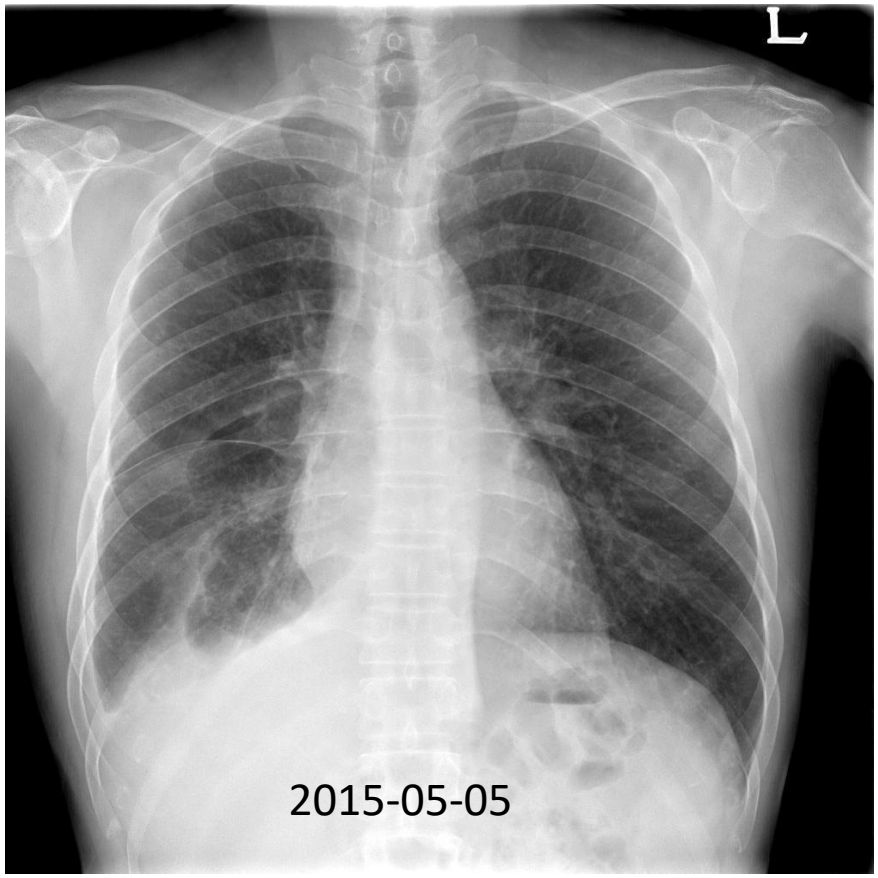


Lung Cancer 2017;106:58-66

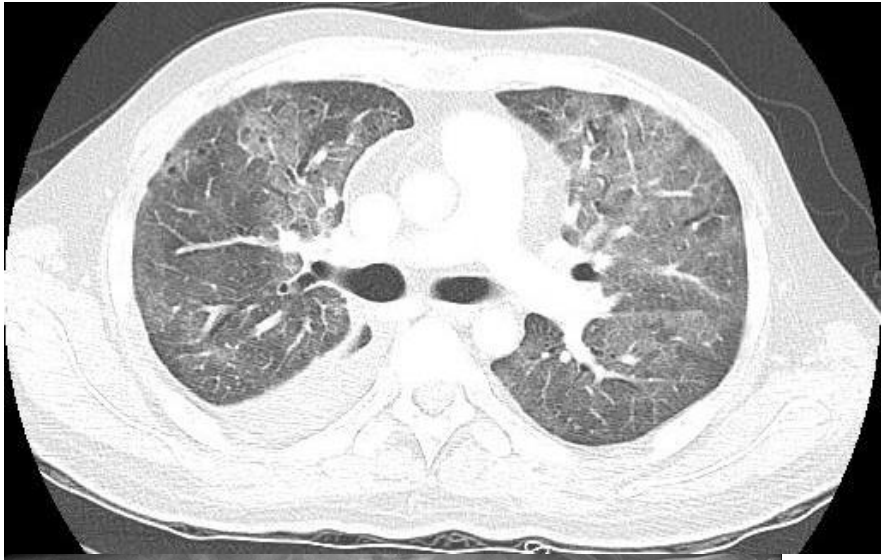
43/M, ALK FISH(+)

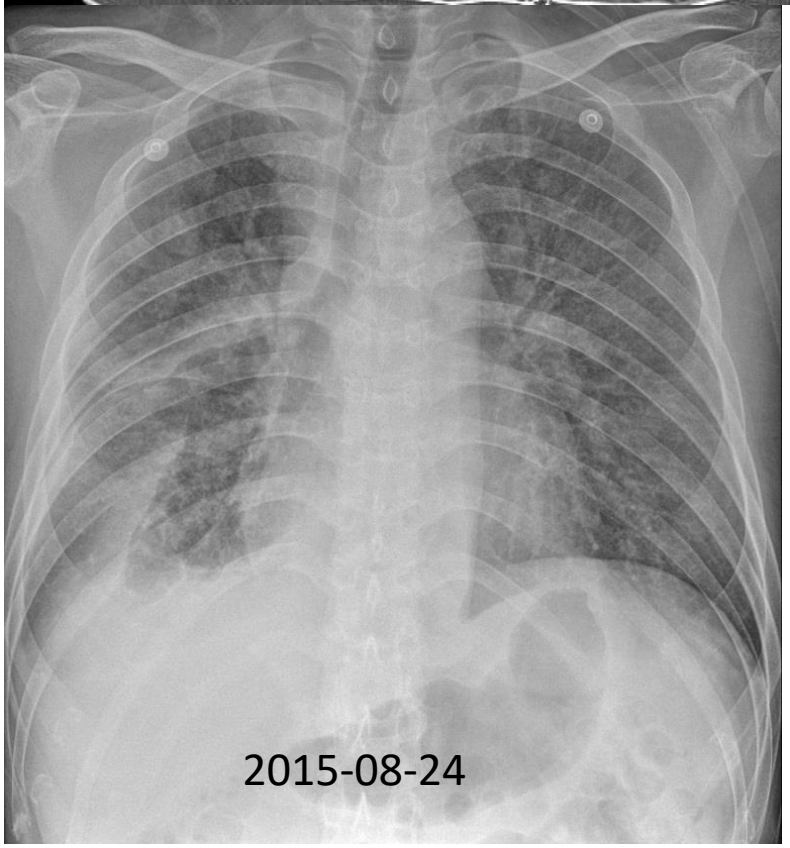
ADC(2013.11.12, AMC) IV - brain mets

- 1Xalkori : 2013.12.3 ~ 2015.4.8
- F-T craniotomy & TR: 2013.11.18
- WBRT: 2014.7.31 ~ 8.31, 10 fx
- 2AP1: 2015.4.15 ~ 5.7 * PD on brain
- *3Xalkori double dose*: 2015.5.7 ~ 8.1
- WBRT: 2015.5.12 ~ 5.28

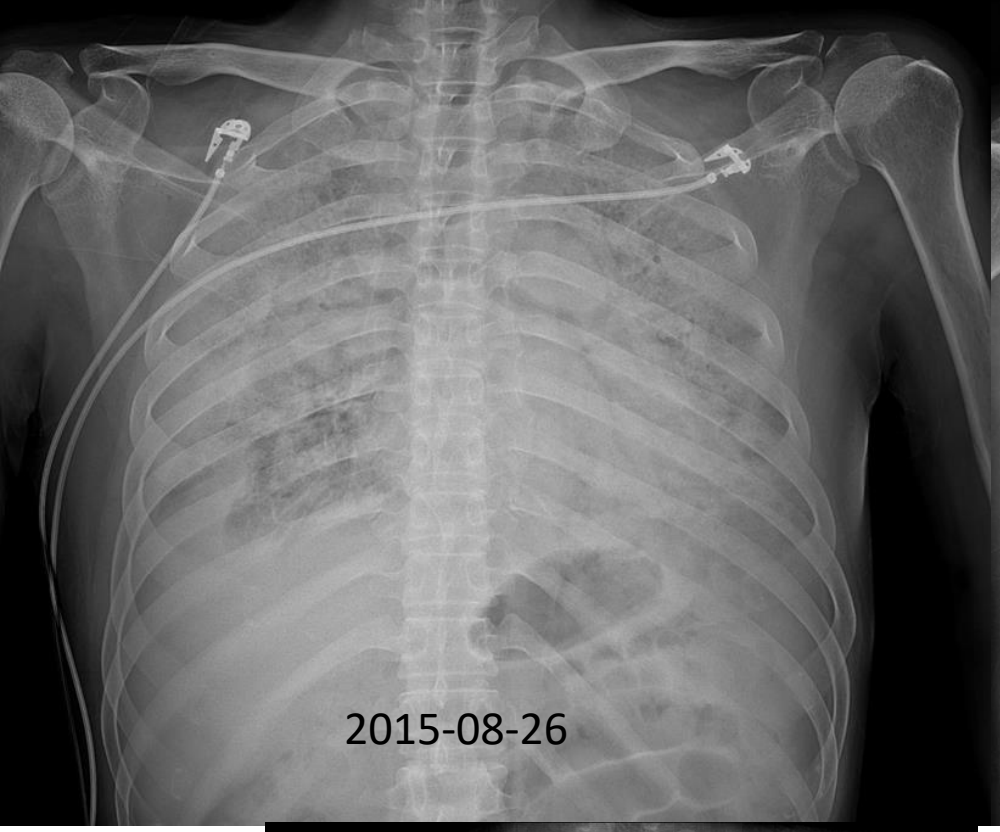


2015-05-05





2015-08-24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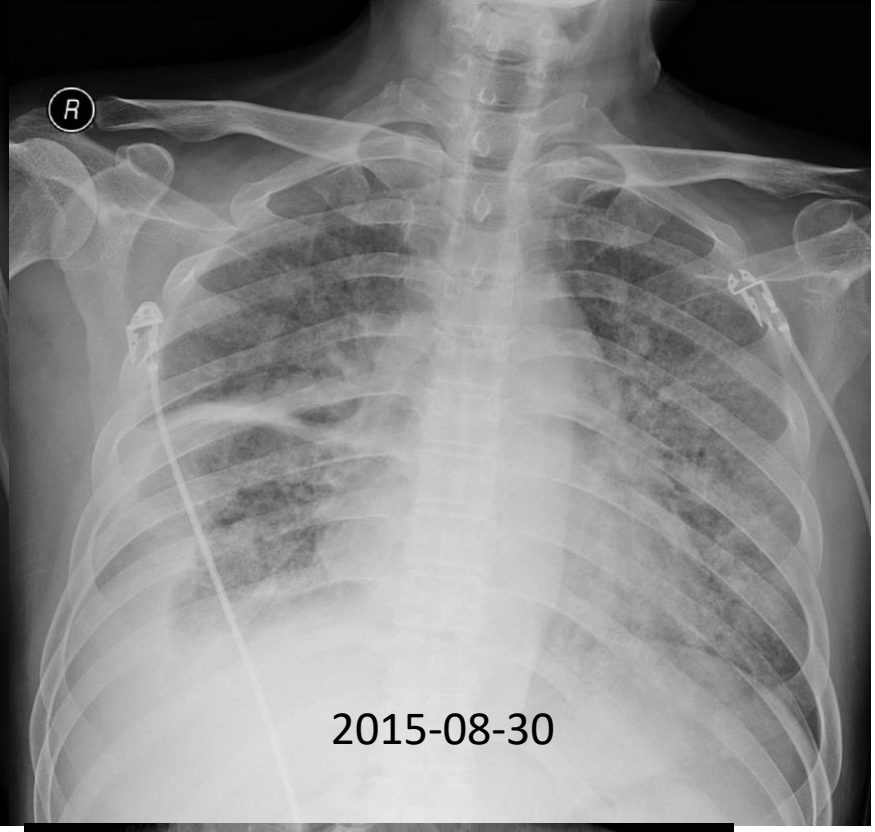
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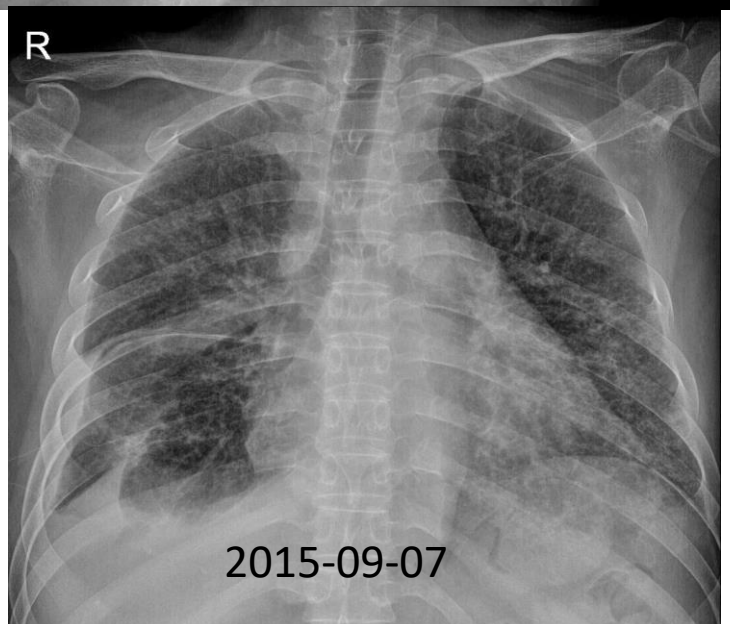
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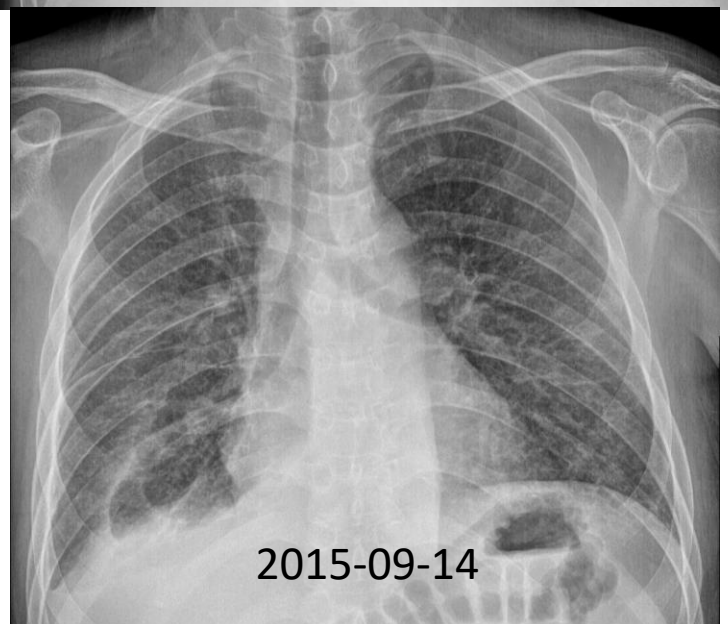
2015-09-14

Drug-induced Interstitial Lung Disease (DILD)

Drugs	Incidence (%)	Fatality (%)	Onset timing
Gefitinib*	1% [Asian 2~6%, Caucasian 0.2~0.3%]	30%	2~3 months
Erlotinib**	0.8%	30%	47 days [5 days ~ 9 months]
Afatinib***	0.5 ~ 1%		
Osimertinib***	2~3%	15%	
Crizotinib	3%	1.5%	3 months
Ceretinib	4% [Grade ≥ 3: 3%]	1%	
PD1/PDL1 inhibitors	5% [Similar in melanoma and NSCLC]		2.8 months [9 days ~ 19 months]
Docetaxel /Paclitaxel****	Grade ≥ 3: 1~5%		
Gemcitabine Irinotecan*****	1~2%		

*Am J Respir Crit Care Med 2008;177:1348, J Clin Oncol 2009;27:5620, Oncologist 2003;8:303.
**Lung Cancer 2014;86:201
***J Clin Oncol 2013;31:3327, Lancet Oncol 2014;15:213.
****Swiss Med Wkly 2002;132:17, J Cancer Res Clin Oncol 2011;137:1469.
*****Oncology 2004;66:94.

Recommended Monitoring in Patients Taking ALK inhibitors

Adverse Event	Baseline Testing	Regular Monitoring
Hepatotoxicity	**AST, ALT, ALP, bilirubin**	Every 2 weeks during the first 2 months, then monthly and as clinically indicated. More frequent testing for grade 2, 3 or 4 elevation
Haematological effects	**CBC and differential**	Monthly and as clinically indicated. More frequently if grade 3 or 4 abnormalities observed, or if fever or infection occurs
Cardiac (QTc prolongation and bradycardia)*	Concomitant medications, physical exam (**heart rate** and **blood pressure**), **EKG**, **electrolytes**	Concomitant medications, physical exam (heart rate and blood pressure). Periodic monitoring for patients at risk of abnormalities with EKG and electrolytes
Ophthalmological**		If persistent or severe symptoms, consider ophthalmological evaluation
ILD/pneumonitis	None	Chest CT, pulmonary function test if indicated by symptoms
Hypogonadism	**Serum testosterone**	If symptomatic, serum testosterone

**Cardiac monitoring may not be needed with alectinib; **Ophthalmological adverse events are specific to crizotinib.*
Adapted from Rothenstein and Letarte, 2014.

Rolfo C, et al. *Eur Oncol Haematol.* 2015;11(2):1-6.