

# 肺癌病歷用藥討論

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1

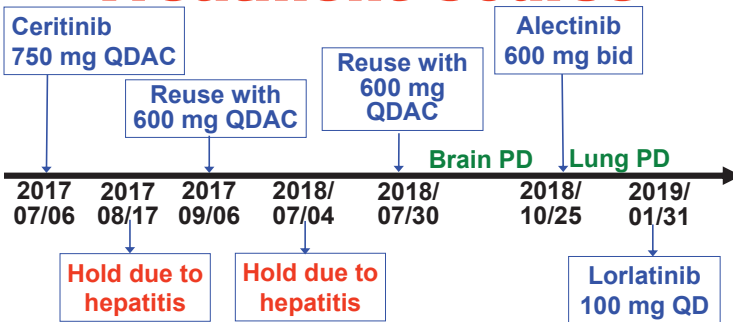
# Case Report

Mrs. L 55 y/o 154.3 cm 54.5 kg BSA=1.53

- **Present illness**
  - RLL adenocarcinoma, with bone, liver and brain metastasis, cT4N3M1b (stage IV), ALK IHC+, under lorlatinib since 2019/1/31
  - Suspect increased intracranial pressure due to leptomeningeal spreading of tumor, s/p lumbar puncture on 2018/10/25
- **Past history**
  - Type 2 diabetes mellitus
  - Dermatofibroma over left thigh
- **Personal history**
  - Smoke (-), alcohol (-)

2

## Treatment Course



### Liver Function

	2017/6/30	2017/8/16	2017/9/6	2018/7/4	2018/7/30
ALT	25	525	79	132	47
AST	25	338	52	117	30
BILIT	0.67	0.77	0.40	0.41	0.82

PD: progression disease

3

## Case Report -2

### Objective

日期	CREA	ALT	AST	Chol	TG	WBC	Hgb	PLT
2019/01/30	-	18	24	212	313	14400	10.7	271K
2019/02/27	-	25	36	455	279	-	-	-
2019/04/09	-	19	26	286	238	-	-	-
2019/05/07	0.62	20	22	302	217	-	-	-

- Brain MRI (2019/5/3): improved

### Drug Profile

藥名/含量/劑量/頻次		01/31	03/13	04/10	05/08
Lorviqua (lorlatinib) cap 25 mg	4# qd	PO			
Ultracet (acetaminophen/tramadol) tab	1# q6hprn	PO			
Celecoxib cap 200 mg	1# qd	PO			
Glucophage (metformin) tab 500 mg	1# bidcc	PO			
Nesina (alogliptin) tab 25 mg	1# qd	PO			
Crestor (rosuvastatin) tab 10 mg	1# qd	PO			

4

## Case Report -3

### Assessment

- Lorlatinib for NSCLC with brain metastases
- Suspected of lorlatinib related hypercholesterolemia

### Plan to do

- Keep current drug therapy
- Suggest follow up blood lipid profile, liver function, WBC and EKG

NSCLC: non-small cell lung cancer; WBC: whole blood count; EKG: electrocardiography

5

## Discussion

### Lung cancer patients with ALK rearrangement

- Introduction
- Target therapy: crizotinib, ceritinib, alectinib, lorlatinib
- Treatment strategy
- **ALK inhibitors in lung cancer patients with brain metastasis**
- **Management of common side effects in ALK inhibitors**
  - Liver toxicity
  - Lorlatinib related hyperlipidemia

6

# ALK+ in Lung Cancer

## Prevalence

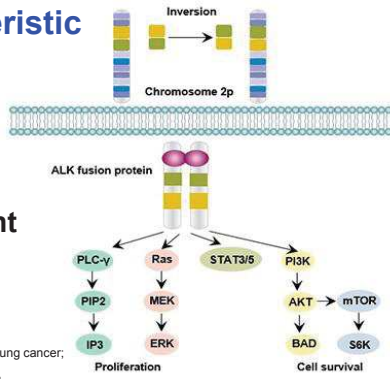
- 3-7% of patients with NSCLC

## Common characteristic

- Younger age
- Never-smokers
- Adenocarcinoma

## Mechanism

- ALK rearrangement
- EML4-ALK fusion gene variation



ALK: anaplastic lymphoma kinase; NSCLC: non-small cell lung cancer; EML4: echinoderm microtubule associated protein like 4  
Singhi EK, et al. 2019;39. <https://www.cusabio.com/c-20917.html>

7

# ALK Inhibitors-1

Generic name	Crizotinib	Ceritinib	Alectinib	Lorlatinib
Trade name	Xalkori®	Zykadia®	Alecensa®	Lorviqua®
<b>Generation</b>	1st	2nd	2nd	3rd
<b>Target</b>	ALK, c-MET, ROS1, RON	ALK, IGF-1R, InsR, ROS1	ALK, RET	ALK, ROS1
<b>Indication</b>	ALK+ or ROS1+ advanced NSCLC	ALK+ advanced NSCLC	ALK+ advanced NSCLC	ALK+ advanced NSCLC with progression on alectinib/ceritinib
<b>Dosage</b>	250 mg bid	450 mg qd	600 mg bid	100 mg qd
<b>Side effect</b>	ALT/AST↑ (61-79%), N/V (46-56%), visual disturbance (60-71%), bradycardia (5-14%)	ALT/AST↑ (75-91%), anemia (67-84%), N/V (35-80%), QT interval prolongation (4-12%)	Anemia (56%), ALT/AST↑ (34-51%), CK ↑ (43%), BG ↑ (36%), bradycardia (18%)	Cholesterol↑ (96%), TG↑ (90%), anemia (52%), ALT/AST↑ (28-37%), peripheral neuropathy (47%), AV block (1%)

c-MET: Hepatocyte growth factor receptor; HGFR.ROS1: c-Ros oncogene 1. RON: Recepteur d'origine nantais. IGF-1R: Insulin-like growth factor 1 receptor; InsR: Insulin receptor. RET: Rearranged during transfection; N/V: nausea and vomit; CK: creatine phosphokinase; BG: blood glucose; TG: triglyceride

8

# ALK Inhibitors-2

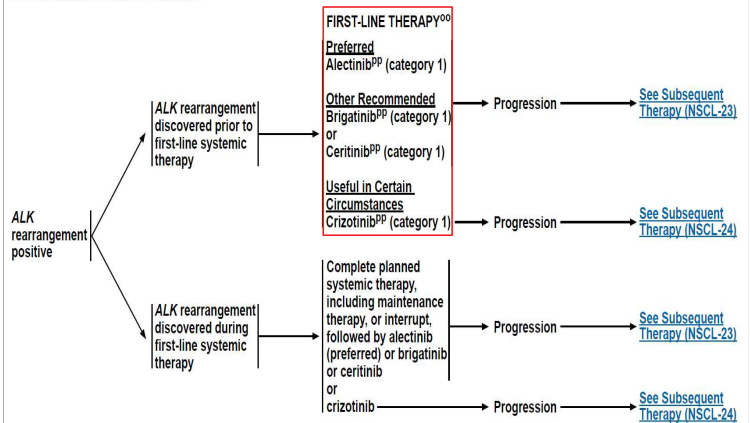
Generic name	Crizotinib	Ceritinib	Alectinib	Lorlatinib
Trade name	Xalkori®	Zykadia®	Alecensa®	Lorviqua®
<b>Liver impairment</b>	Mild (BILIT 1.5-3 x ULN): 200 mg bid Severe (BILIT>3x ULN): 250 mg qd	Severe (Child-Pugh C): decrease 1/3 dose, rounded to the nearest multiple of the 150 mg strength	Severe (Child-Pugh C): 450 mg bid	Moderate/severe: NA
<b>ClCr &lt; 30 ml/min</b>	250 mg qd	NA	NA	NA
<b>Contra-indication</b>	Congenital long QT syndrome or persistent QTcF ≥500 msec	-	-	Concomitant use of strong CYP3A inducers
<b>健保價 (元/日)</b>	5124	2865	3320	6400 (售價)

BILIT: total bilirubin; ClCr: creatinine clearance; HD: hemodialysis; NA: not available

9

# ALK inhibitor in Advanced NSCLC-1

ALK REARRANGEMENT POSITIVE<sup>§</sup>

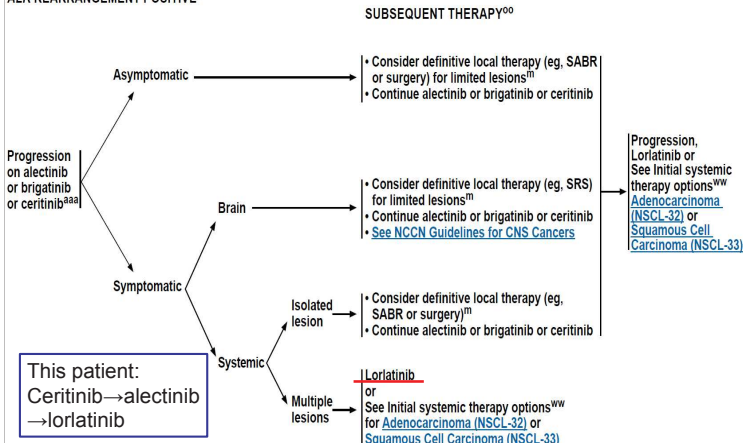


National Comprehensive Cancer Network (NCCN) NSCLC v.5. 2020

10

# ALK inhibitor in Advanced NSCLC-2

ALK REARRANGEMENT POSITIVE<sup>§</sup>



National Comprehensive Cancer Network (NCCN) NSCLC v.5. 2020

11

# 健保給付規定

Crizotinib (Xalkori®)	Ceritinib (Zykadia®)	Alectinib (Alecensa®)
適用於ALK陽性或ROS-1陽性之晚期非小細胞肺癌患者。	適用於ALK陽性之晚期非小細胞肺癌。	適用於ALK陽性之晚期非小細胞肺癌。
每日最大劑量限500mg。	每日最大劑量限450mg。	每日最大劑量限1200mg。
須經事前審查核准後使用		
用於ALK陽性之晚期非小細胞肺癌時，三者僅得擇一使用，除因病人使用後，發生嚴重不良反應或耐受不良之情形外，不得互換。		

12

## ALK+ and Brain Meta

- **Prevalence**
  - 20-35% present with brain meta in newly diagnosis
- **Poor prognosis**
  - Neurocognitive and functional deficits
  - 60% develop BM during crizotinib
- **Symptomatic palliative treatment**
  - Steroids and anti-epileptic drugs
- **Local therapies**
  - Surgical resection, stereotactic radiosurgery, and WBRT
- **Median OS**
  - Without treatment: 3 months
  - ALK inhibitor + WBRT : 49.5 months

BM: brain metastases; OS: overall survival; WBRT: whole brain radiotherapy  
Lung Cancer. 2019;129:63-71. J Clin Oncol. 2016;34:107-9.

13

## ALK Inhibitors in CSF

Compound	Plasma concentration	CSF concentration	CSF penetration rate
Crizotinib	237 ng/mL	0.616 ng/mL	0.26%
Alectinib	3.12 nM	2.69 nM	86%
Ceritinib	NA	NA	15%
Lorlatinib	NA	NA	75%

CSF: cerebrospinal fluid

Wrona A. Cancer Radiother. 2019;23:432-438.

14

## 2nd ALK Inhibitors for Brain Meta

Table 2. Frequency of brain metastasis in the trials regarding ALK inhibitors and efficacy of ALK inhibitors for brain metastasis in patients with ALK-positive NSCLC

Treatment	Patients, n	BM n (%)	CNS RR (%)	CNS DCR (%)	Duration of CNS response (months)	Reference
Crizotinib	888	275 (31)	25	56	7	Costa et al. [17]
Ceritinib	246	124 (50.4)	34.5	50.6	6.9	Shaw et al. [24]
Ceritinib	140	100 (71.4)	30.6	77.1	6.9	Mok et al. [25]
Ceritinib	124	50 (40.3)	63.7	89.5	11.1	Felip et al. [26]
Alectinib	87	52 (60)	75	100	11.1	Shaw et al. [32]
Alectinib	130	84 (61)	57.1	83	10.3	Ou et al. [33]

BM: brain metastasis, N: number of patients, RR: response rate, DCR: disease control rate, CNS: central nervous system, NSCLC: non small cell lung cancer, NR: not reported

- **Alectinib reduced BM incidence**
- **Combining WBRT**
  - In crizotinib-refractory patients: only little curative effect

BM: brain metastases; WBRT: whole brain radiotherapy  
Muhammet Hacıoglu B, et al. J BUON. 2017;22:586-91. Wang W, et al. Oncol Res Treat. 2019;42:599-606.

15

## Lorlatinib for Brain Meta

	Post-crizotinib	Post-2nd-Generation ALK inhibitor	≥2 previous ALK inhibitor
IC-ORR, % (95%CI)	87% (66.4-97.2)	55.6% (21.2-86.3)	53.1% (38.3-67.5)
Median IC-DOR, NR (8.4 - NR) month (95%CI)		NR (4.1 - NR)	14.5 (6.9 -14.5)

- **Leptomeningeal Carcinomatosis**
  - IC-ORR 45%; IC-DCR: 91% (59-100)
  - Median PFS: 9.3 months (1.0-NR)
  - 12-month PFS rates: 50.0% (12.6-79.3)

IC: Intracranial; ORR: objective response rate; DOR: duration of response; NR: not reached; DCR: disease control rate; PFS: progression free survival; DOT: duration of treatment  
Zhu VW, et al. J Thorac Oncol. 2020;S1556-0864: 30334-8.

16

## Recommended Dosage Reduction Levels

	Crizotinib Xalkori®	Ceritinib Zykadia®	Alectinib Alecensa®	Lorlatinib Lorviqua®
Initial	250 mg bid	450 mg QDCC	600 mg bid	100 mg QD
First reduction	200 mg bid	300 mg QDCC	450 mg bid	75 mg QD
Second reduction	250 mg QD	150 mg QDCC	300 mg bid	50 mg QD

Discontinue if unable to tolerate after second reduction

17

## Managing Liver toxicity

Crizotinib Xalkori®	Ceritinib Zykadia®	Alectinib Alecensa®	Lorlatinib Lorviqua®
ALT/AST >5x ULN: withhold until recovery to baseline or ≤3x ULN, reduced dose	ALT/AST >5x ULN & BILIT ≤2x ULN: withhold until recovery to baseline or ≤3x ULN, reduced dose		Persistent ≥ grade 2 hepatotoxicity during concomitant with moderate CYP3A inducers, discontinue lorlatinib or the CYP3A inducer
ALT/AST >3x ULN & BILIT >1.5x ULN (absence of cholestasis/hemolysis): Permanently discontinue	ALT/AST >3x ULN & BILIT >2x ULN (absence of cholestasis/hemolysis): Permanently discontinue		
BILIT >3x ULN: withhold until recover to baseline/BILIT ≤ 1.5x ULN, reduced dose			

	2017/6/30	07/06	08/16	09/06	2018/07/04	07/30
ALT	25	Start ceritinib	525	Hold due to hepatitis	79	Reuse 600 mg qdac
AST	25	750 mg qdac	338	52	132	Hold due to hepatitis
BILIT	0.67	0.77	0.77	0.40	0.41	0.82

ULN: upper limited normal

18

## Lorlatinib Related Hypercholesterolemia or hypertriglyceridemia

- **Grade 1-3**
  - Continue and keep monitoring cholesterol and TG
- **Grade 4**
  - **Definition:**
    - \* Cholesterol >500 mg/dL
    - \* TG >1000 mg/dL; life-threatening consequences
  - Withhold until recovery  $\leq$  grade 2, resume at same dose
  - Severe adverse effects recurs: resume at a **reduced dose**
- **Any grade**
  - Initiation or increased doses of **lipid-lowering agents**
- **Naranjo score: 5 (probable)**

This patient (2/27):  
Chol: 455 mg/dL (grade 3)

Chol: cholesterol; TG: triglyceride Bauer TM, et al. *Oncologist*. 2019;24:1103-10.

19

## Take Home Message

- **New generation ALK inhibitors is effective in NSCLC ALK+ patients with brain metastases**
- **Common side effects of ALK inhibitors**
  - Liver toxicity, hypercholesterolemia, hypertriglyceridemia, etc.

20

