

肺癌病歷用藥討論

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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 lolartinib since 2019/1/31
- Suspect increased intracranial pressure due to leptomeningeal spreading of tumor, s/p lumbar puncture on 2018/10/25

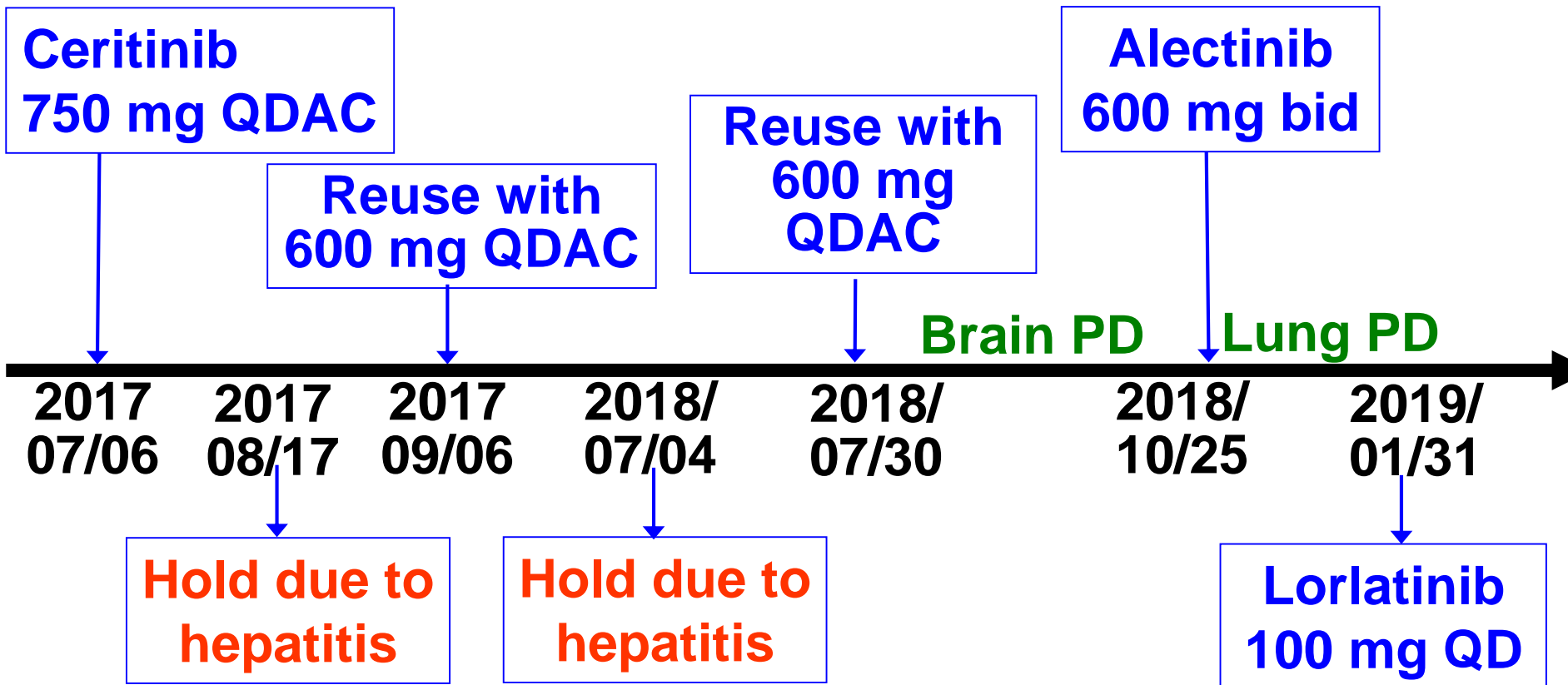
- **Past history**

- Type 2 diabetes mellitus
- Dermatofibroma over left thigh

- **Personal history**

- Smoke (-), alcohol (-)

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

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				

Case Report -3

- **Assessment**

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

- **Plan to do**

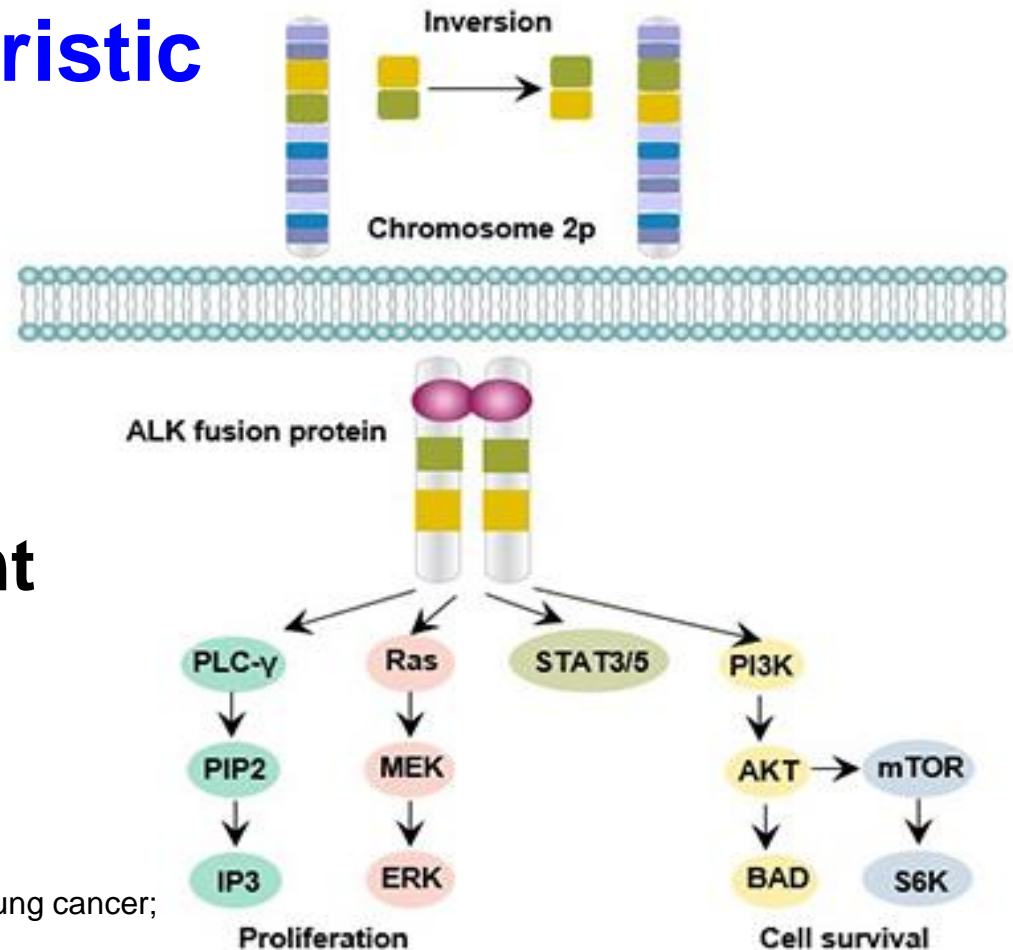
- Keep current drug therapy
- Suggest follow up blood lipid profile, liver function, WBC and EKG

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

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 Inhibitors-1

Generic name	Crizotinib	Ceritinib	Alectinib	Lorlatinib
Trade name	Xalkori®	Zykadia®	Alecensa®	Lorviqua®
Generation	1st	2nd	2nd	3rd
Target	ALK, c-MET, ROS1, RON	ALK, IGF-1R, InsR, ROS1	ALK, RET	ALK, ROS1
Indication	ALK+ or ROS1+ advanced NSCLC	ALK+ advanced NSCLC	ALK+ advanced NSCLC	ALK+ advanced NSCLC with progression on alectinib/ceritinib
Dosage	250 mg bid	450 mg qdcc	600 mg bidcc	100 mg qd
Side effect	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 (8-18%)	Cholesterol↑ (96%), TG↑ (90%), anemia (52%), ALT/AST↑ (28-37%), peripheral neuropathy (47%), AV block (1%)

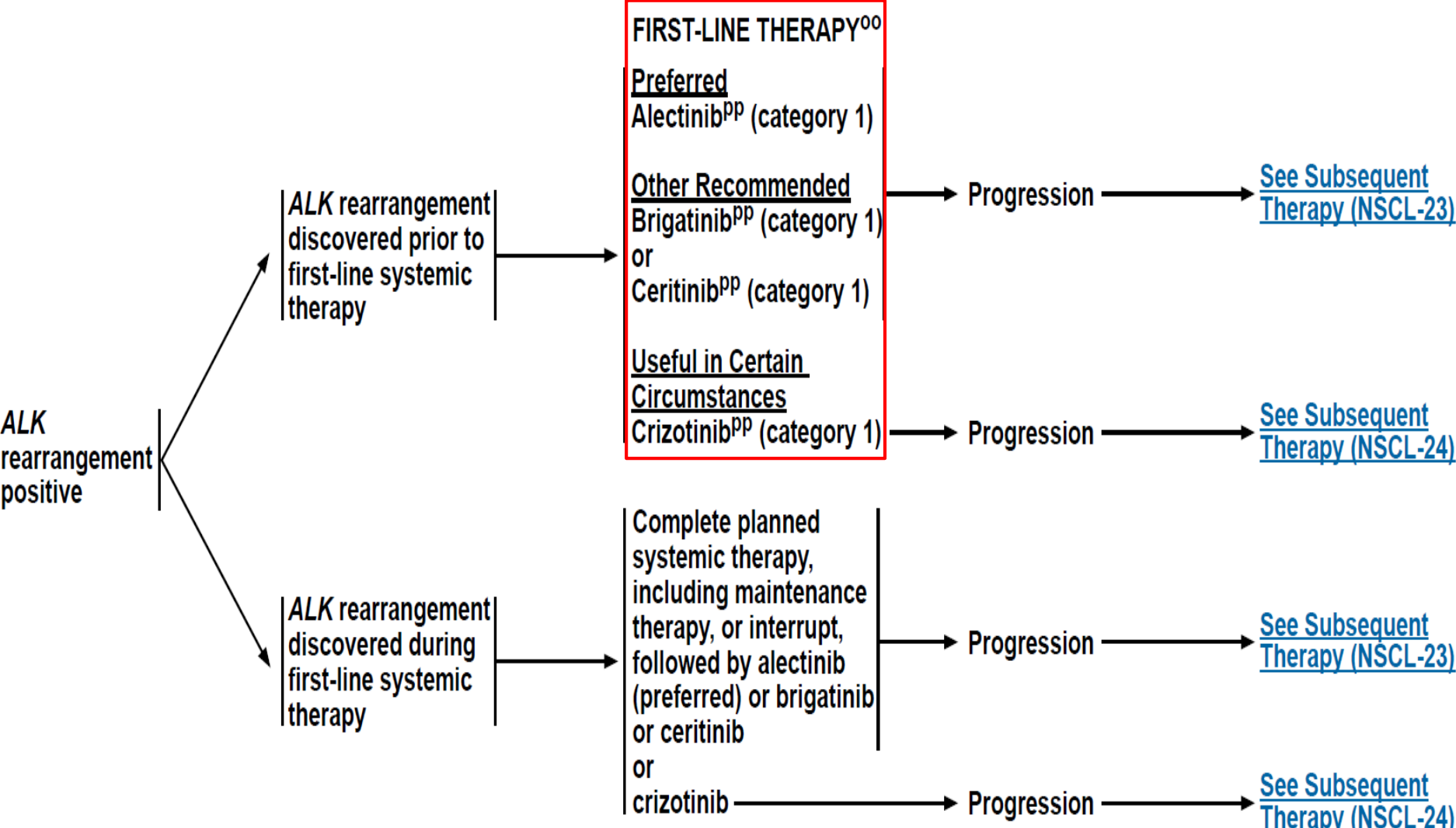
c-MET: Hepatocyte growth factor receptor; HGFR,ROS1: c-Ros oncogene 1, RON: Recepteur d'origine nantais, IGF-1R: Insulin-like growth factor 1 receptor; InsR:Insulin receptor, RET: Rearranged during transfection; N/V: nausea and vomit; CK: creatine phosphokinase; BG: blood glucose; TG: triglyceride

ALK Inhibitors-2

Generic name	Crizotinib	Ceritinib	Alectinib	Lorlatinib
Trade name	Xalkori®	Zykadia®	Alecensa®	Lorviqua®
Liver impairment	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
CICr < 30 ml/min	250 mg qd	NA	NA	NA
Contra-indication	Congenital long QT syndrome or persistent QTcF ≥500 msec		-	Concomitant use of strong CYP3A inducers
健保價 (元/日)	5124	2865	3320	6400 (售價)

ALK inhibitor in Advanced NSCLC-1

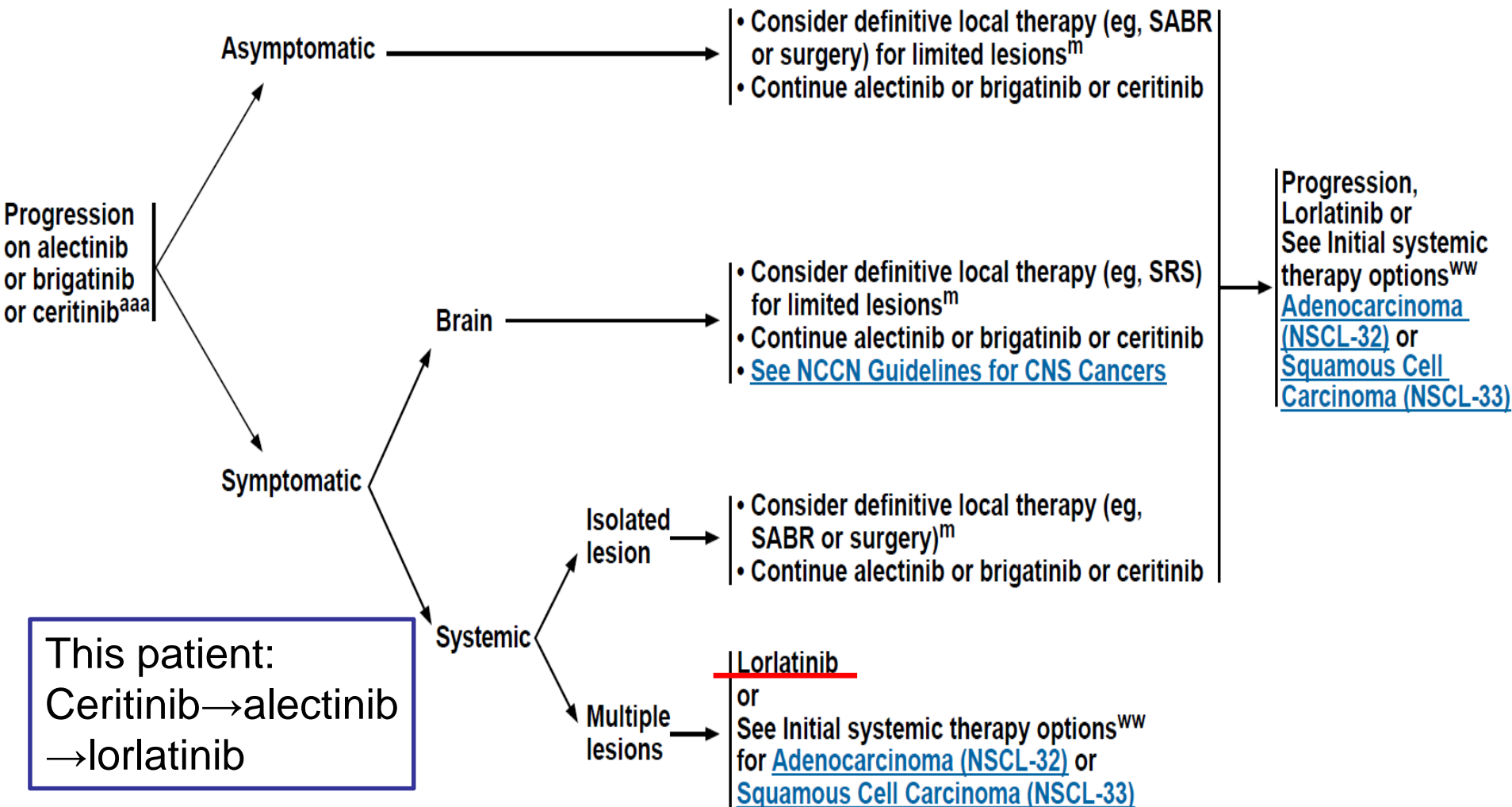
ALK REARRANGEMENT POSITIVE^{ij}



ALK inhibitor in Advanced NSCLC-2

ALK REARRANGEMENT POSITIVE^{ij}

SUBSEQUENT THERAPY^{oo}



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。		

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

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.

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	58.6	6.9	Shaw et al. [24]
Ceritinib	140	100 (71.4)	38.6	77.1	6.9	Mok et al. [25]
Ceritinib	124	50 (40.3)	<u>63.7</u>	<u>89.5</u>	<u>11.1</u>	Felip et al. [26]
Alectinib	87	52 (60)	<u>75</u>	100	11.1	Shaw et al. [32]
Alectinib	138	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 Hacioglu B, et al. *J BUON*. 2017;22:586-91. Wang W, et al. *Oncol Res Treat*. 2019;42:599-606.

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, month (95%CI)	NR (8.4 - NR)	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)

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

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	525	Hold	79	Reuse	132	Hold	47	Reuse
AST	25	ceritinib 750 mg	338	due to hepatitis	52	600 mg qdac	117	due to hepatitis	30	600 mg qdac
BILIT	0.67	qdac	0.77	0.40	0.41	0.82				

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)

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.**

A colorful illustration of a globe. The globe is divided into horizontal bands of color: yellow, green, pink, and blue. The word "Medicine" is written across the globe in large, stylized letters. The letters are colored: 'M' is blue, 'e' is brown, 'd' is yellow, 'i' is orange, 'c' is brown, 'e' is blue, and 'n' is blue. On the globe, there are several figures: a male doctor in a white coat and tie, a female nurse in a white uniform and cap, a patient with a bandage on their head, and a child. There is also a hospital building with a red cross on top, a tree, and a sun with a face in the sky. The background is a light blue sky with clouds.

Thanks for Your Attention