肺癌病歷用藥討論

臺北榮民總醫院藥學部

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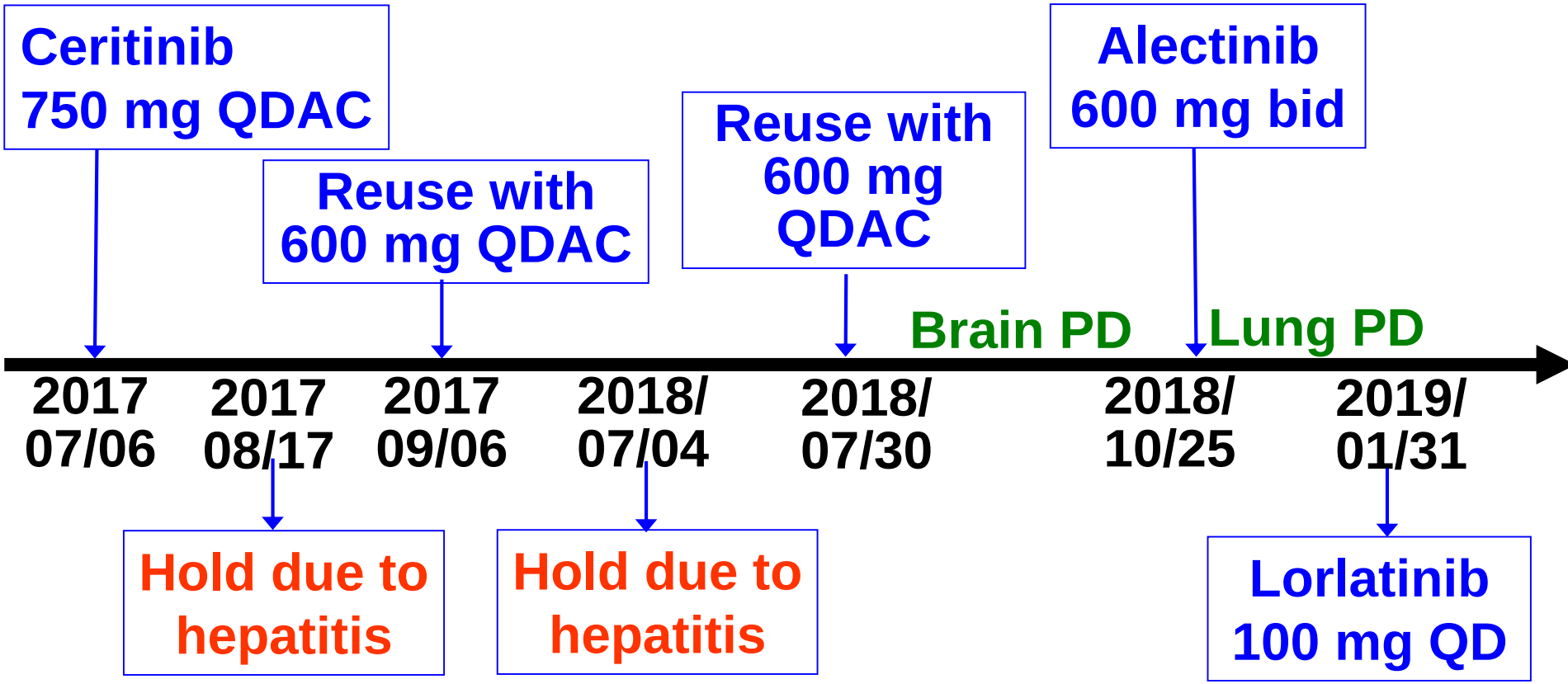
Case Report

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

PD: progression disease

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**

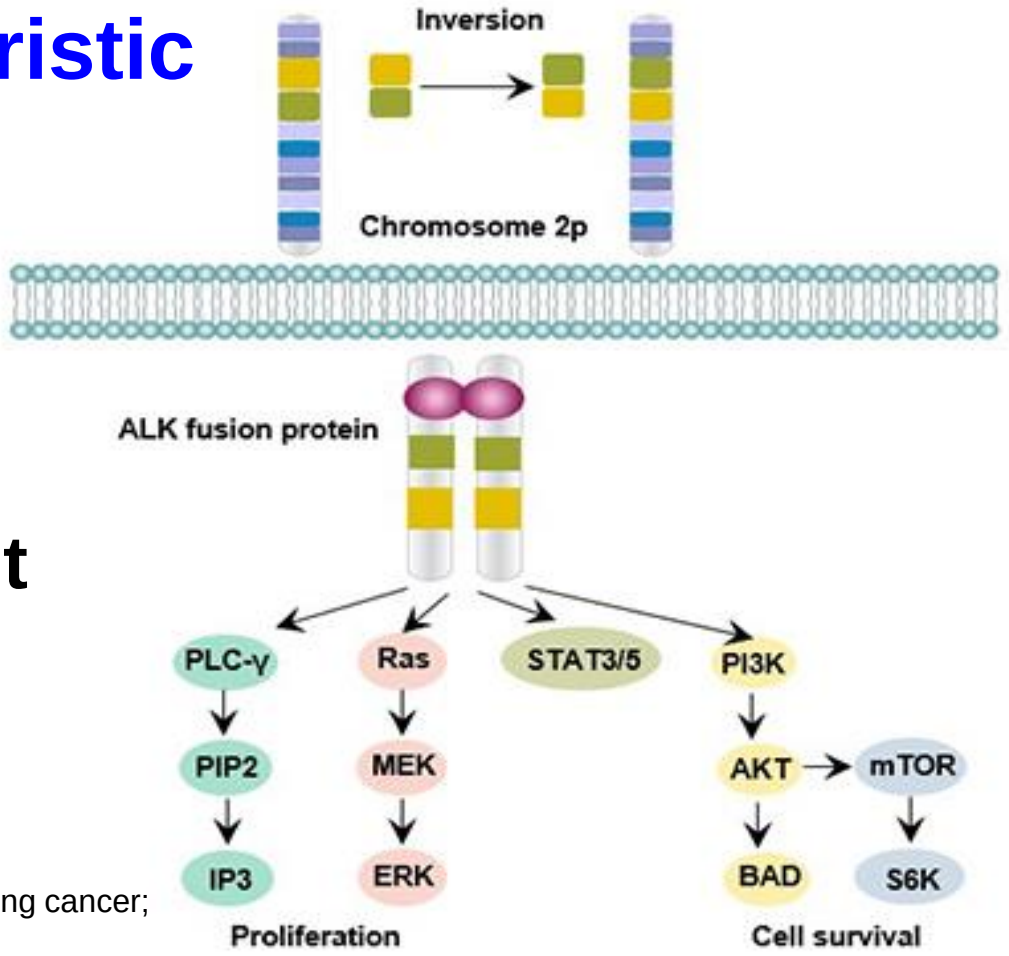
NSCLC: non-small cell lung cancer; WBC: whole blood count; EKG: electrocardiography

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: 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

ALK Inhibitors-1

Generic name Trade name	Crizotinib Xalkori®	Ceritinib Zykadia®	Alectinib Alecensa®	Lorlatinib 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%)

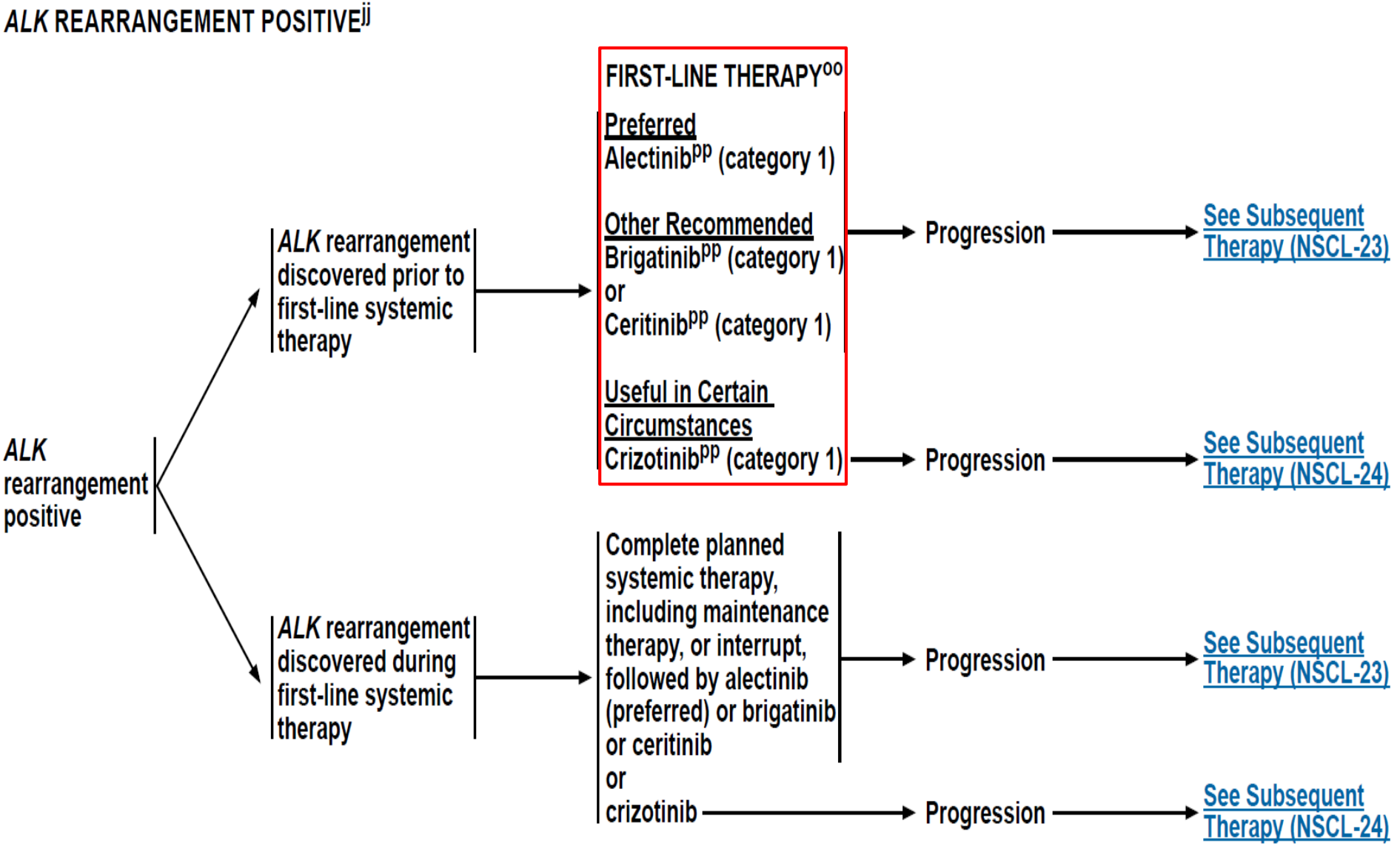
c-MET: Hepatocyte growth factor receptor; HGFR,ROS1: c-Ros oncogene 1, RON: Recepteur d'origine nantais, IGF-1R: Insulin-like growth factor 1 receptor; InsR:Insulin receptor, RET: Rearranged during transfection; N/V: nausea and vomit; CK: creatine phosphokinase; BG: blood glucose; TG: triglyceride

ALK Inhibitors-2

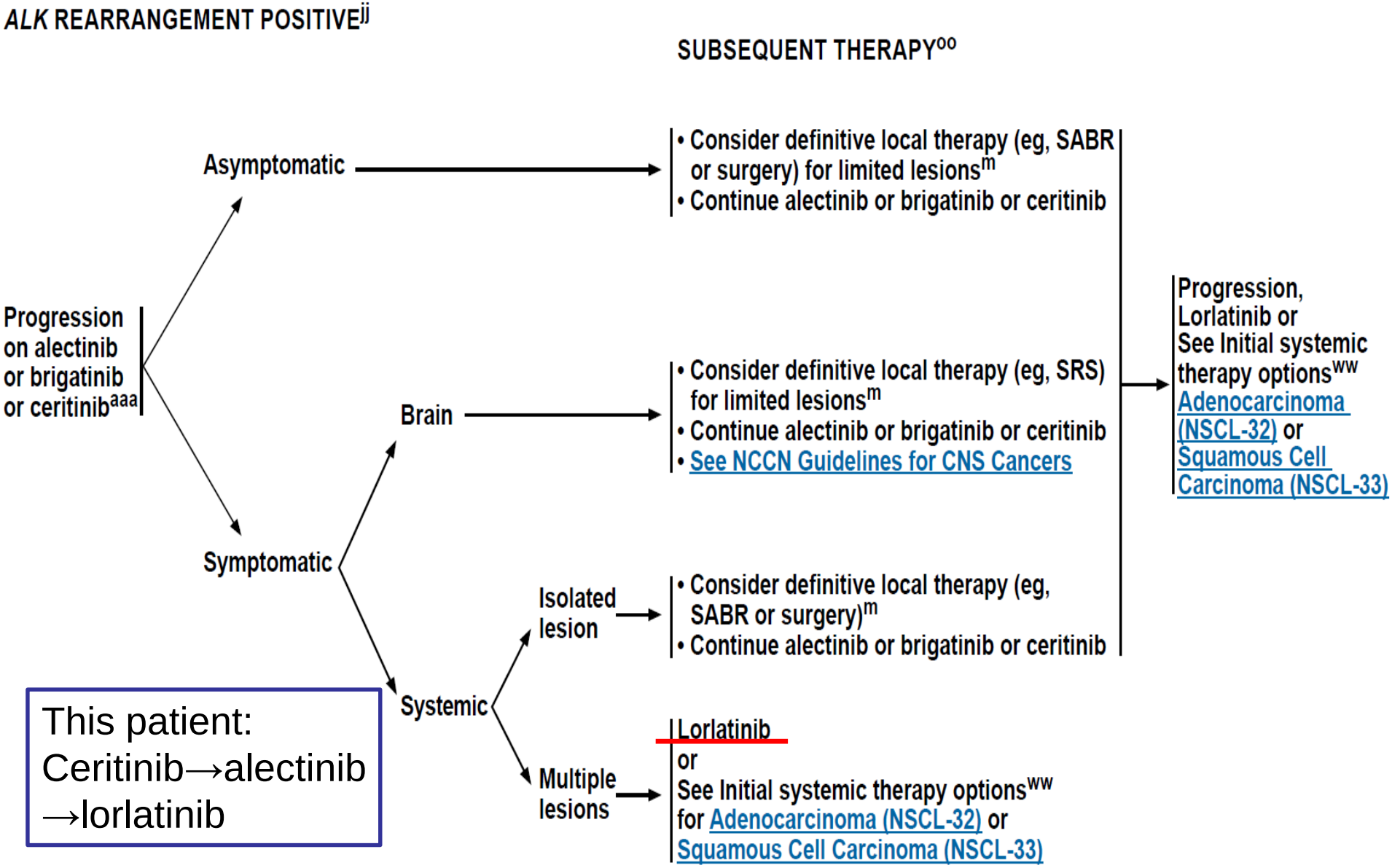
Generic name Trade name	Crizotinib Xalkori®	Ceritinib Zykadia®	Alectinib Alecensa®	Lorlatinib Lorviqua®
Liver impairment	Mild (BILIT 1.5-3 x ULN: 200 mg bid Severe (BILIT>3x ULN): 250 mg qd	Severe (Child-Pugh C): decrease 1/3 dose, rounded to the nearest multiple of the 150 mg strength	Severe (Child-Pugh C): 450 mg bid	Moderate/ severe: NA
ClCr < 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)

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

ALK inhibitor in Advanced NSCLC-1



ALK inhibitor in Advanced NSCLC-2



This patient:
Ceritinib→alectinib →lorlatinib

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**

BM: brain metastases; OS: overall survival; WBRT: whole brain radiotherapy

Lung Cancer. 2019;129:63-71. *J Clin Oncol*. 2016;34:107-9.

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)	63.7	89.5	11.1	Felip et al. [26]
Alectinib	87	52 (60)	75	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)**

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.

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

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

	2017/6/30		07/06		08/16		09/06		2018/07/04		07/30	
ALT	25		Start ceritinib 750 mg qdac		525	Hold due to hepatitis	79	Reuse 600 mg qdac	132	Hold due to hepatitis	47	Reuse 600 mg qdac
AST	25	→		→	338		52		117		30	
BILIT	0.67				0.77		0.40		0.41		0.82	

ULN: upper limited normal

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 ≤ 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.

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.

Thanks for Your Attention