Front-line treatment of ceritinib improves efficacy over crizotinib for Asian patients with anaplastic lymphoma kinase fusion NSCLC: The role of systemic progression control

Shih-Hao Huang†, Allen Chung-Cheng Huang†, Chin-Chou Wang2, Wen-Chen Chang3, Chien-Ying Liu1, Stelios Pavlidis3, Ho-Wen Ko1, Fu-Tsai Chung1, Ping-Chih Hsu1, Yi-Ke Guo4, Chih-Hsi Scott Kuo1,4 & Cheng-Ta Yang1

1 Division of Thoracic Oncology, Department of Thoracic Medicine, Chang Gung Memorial Hospital, Chang Gung University, College of Medicine, Taipei, Taiwan
2 Division of Pulmonary & Critical Care Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan
3 Department of Medical Oncology, Chang Gung Memorial Hospital, Chang Gung University, Taipei, Taiwan
4 Data Science Institute, Department of Computing, Imperial College London, London, UK

Keywords
ALK; ceritinib; crizotinib; NSCLC.

Correspondence
Chih-Hsi Scott Kuo, Department of Thoracic Medicine, Chang Gung Memorial Hospital, No. 199, Tun-Hwa North Road, Taipei, Taiwan. Tel.: +886 3 328 1200 Fax: +886 3 328 3141 Email: chihhsikuo@gmail.com

†Equal contribution.

Received: 29 August 2019; Accepted: 26 September 2019.

doi: 10.1111/1759-7714.13221

Introduction
Advanced non-small cell lung cancer (NSCLC) is a deadly disease with a dismal prognosis.1 However, a treatment strategy targeting the inhibition of driving mutations has revolutionized the survival in some patients.2 One specific patient group which has experienced a dramatic improvement in survival are those patients with anaplastic lymphoma kinase (ALK) fusion NSCLC who receive treatment with ALK tyrosine kinase inhibitors (ALKi).

Abstract
Background: Approximately 3%–5% of lung adenocarcinoma is driven by anaplastic lymphoma kinase (ALK) fusion oncogene, whose activity can be suppressed by multiple ALK inhibitors. Crizotinib and ceritinib have demonstrated superior efficacy to platinum-based chemotherapy as front-line treatment for patients with ALK-positive advanced non-small cell lung cancer (NSCLC). However, the direct comparison between them in the front-line setting remains lacking.

Methods: A total of 48 patients with ALK-positive, previously untreated advanced NSCLC, who received crizotinib and ceritinib as front-line treatment were retrospectively investigated. The efficacy and pattern of disease progression were analyzed.

Results: Patients receiving ceritinib treatment were significantly younger than those receiving crizotinib treatment (52.0 vs. 63.0, P = 0.016). The median progression-free survival (PFS) was significantly longer with ceritinib than with crizotinib treatment (32.3 vs. 12.9 months; log-rank P = 0.020); the hazard ratio for disease progression or death, 0.27 (95% CI, 0.08–0.90; P = 0.033). An objective response was noted in all patients in the ceritinib group and in 23 patients in the crizotinib group (74.2%; 95% CI, 59.0 to 88.5). The rate of systemic progression was significantly lower over time with ceritinib treatment compared to crizotinib treatment (cause-specific hazard ratio, 0.21; 95% CI 0.06–0.73; P = 0.014). Serious adverse events were noted in one (2.9%) patient showing elevated liver function in the crizotinib group and three (23.1%) patients showing diarrhea in the ceritinib group. Dose reduction was needed in five out of 13 (38.5%) patients receiving ceritinib treatment.

Conclusion: Ceritinib showed higher efficacy associated with a better control of systemic progression compared to crizotinib for the front-line treatment of ALK-positive advanced NSCLCs.
Crizotinib, the first FDA-approved ALKi for the treatment of advanced ALK-positive NSCLC, has shown superior efficacy compared to the standard of care chemotherapy docetaxel and pemetrexed-cisplatin doublet in the second- and first-line setting, respectively.\textsuperscript{3,4} Disease progression usually occurs around 10 to 12 months during crizotinib treatment where the pattern of progression involves a high frequency of brain metastasis which targets the brain as a sanctuary site.\textsuperscript{5,6} This finding can be partly attributed to the drug transporters located at the blood brain barrier that actively efflux the therapeutic drugs and thereby reduce their concentrations in the brain tissue.\textsuperscript{7} A previous study in a mouse model indicated that gene knockout mice lacking the drug transporters P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2) had a 20- to 70-fold higher brain accumulation of crizotinib than their wild-type counterparts.\textsuperscript{8} In light of this, the second generation ALKi alectinib, which is not a substrate of the drug transporters ABCB1 and ABCG2, has shown superior efficacy over crizotinib in comparative studies.\textsuperscript{9,10} This advantage over crizotinib was mainly attributed to a lower incidence of brain progression during the treatment of alectinib, whereas the incidence of systemic progression between the two drugs was similar.\textsuperscript{10}

Apart from alectinib which features a promising brain tissue penetration, another second generation ALKi ceritinib is characterized by a relatively high potency against ALK tyrosine kinase compared to crizotinib and alectinib.\textsuperscript{11,12} Ceritinib was the first FDA-approved second generation ALKi for the treatment of ALK-positive NSCLC. It has shown promising efficacy over chemotherapy for patients with disease progression from crizotinib treatment and also patients who have not been previously treated.\textsuperscript{13,14} Given the high potency of ceritinib, both against wild-type ALK as well as a number of gatekeeper mutations,\textsuperscript{15} ALK-positive NSCLC patients treated with ceritinib may have a better control of systemic progression than those treated with crizotinib, albeit evidence of the direct comparison between the two drugs is scarce.

On the other hand, the adequate penetration of ceritinib to brain tissues for the control and prevention of brain metastasis remains a controversial issue. A previous study of a mouse model had shown that the penetration of ceritinib, as measured by the ratio of plasma to cerebral spinal fluid concentration, was only around 15% in which the active efflux of ceritinib by the drug transporters ABCB1 and ABCG2 still accounted for its reduced penetration to brain tissues.\textsuperscript{16} This finding may also partly be associated with a diverse intracranial efficacy of ceritinib, as the intracranial objective response rate of brain metastasis ranged between 40% to 70% for ALKi-naïve patients who received ceritinib treatment.\textsuperscript{14,17,18}

In the meantime, no dedicated clinical trial which directly compares the therapeutic outcome between ceritinib and crizotinib is available, except a few reports which indirectly compare the two drugs using the patients that propensity score-matched from individual clinical trials originally conducted for the study of crizotinib and ceritinib, respectively.\textsuperscript{19,20} These indirect comparisons are insightful for the analysis of the primary outcomes consistently defined across the original trials, such as progression-free or overall survival, although they might not be feasible for the analysis of the outcomes, such as the pattern of disease progression, as these were not consistently defined across the trials. In this study, we retrospectively compared a group of patients who received either crizotinib or ceritinib as the front-line treatment and the treatment efficacy, pattern of disease progression and toxicity profile were analyzed.

**Methods**

**Patients**

Between January 2015 and August 2018, a total of 110 patients with advanced or metastatic ALK fusion NSCLCs diagnosed by Ventana ALK (D5F3) CDx immunohistochemistry assay (Roche Diagnostics, USA) at Chang Gung Memorial Hospital were retrospectively reviewed using Chang Gung Research Database. A total of 48 patients had ALK inhibitors as the front-line treatment, in which 35 patients received crizotinib 250 mg twice daily and 13 patients received ceritinib 750 mg or 450 mg once daily. Progression-free survival (PFS) was defined as the interval between the date of the start of ALK inhibitors and the date of either radiologically-documented progression or death. The treatment response, defined as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The pattern of post-ALK inhibitor disease progression was also reviewed and defined as either systemic progression without prior CNS progression/death or CNS progression without prior systemic progression/death. The toxicities noted during ALK inhibitor treatment were systematically reviewed and the toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 5.0. The study was approved by the Ethics Committee of Chang Gung Memorial Hospital.

**Statistical analysis**

The Mann-Whitney test was used to determine the statistical significance between two groups of continuous variables; Fisher’s exact tests were used for categorical variables. The Kaplan-Meier survival curve was analyzed using the R package survival, and the hazard ratio was analyzed using the Cox regression model. For the propensity
score matching analysis, the ceritinib versus the crizotinib
group served as the dependent variable; the covariates used
included age, smoking history, Eastern Cooperative Oncol-
gy Group performance status (ECOG PS) and brain
metastasis. The coefficient for each covariate was deter-
mained by logistic regression analysis, and the propensity
score of each individual was calculated as the sum of the
product of each coefficient and the value of each covariate.
The pairs of ceritinib and crizotinib individuals with equiva-
alent propensity scores were selected in a 1:2 manner using
the R package MatchIt. The patterns of post-ALK inhibitor
disease progression were treated as competing risk events
of which the cumulative incidence functions were calcu-
lated.21 The modified Cox regression model for the sub-
distribution hazard of the cumulative incidence function
was applied22 to calculate the hazard of disease progression
from a given pattern in the presence of competing event
using the R package cmprsk. All the reported P-
values were two-sided, and a P-value less than 0.05 was consid-
ered to be statistically signi-
cificant. All the data were ana-
lyzed using SPSS 10.1 (SPSS Corp., Chicago, IL, USA).

Results

Baseline patient characteristics
Clinical data from 48 patients of ALK fusion advanced or
metastatic NSCLC receiving
firstline ALK inhibitor treat-
ment (35 in the crizotinib group and 13 in the ceritinib
group) were extracted from the Chang Gung Research
Database. Most of the baseline clinical characteristics,
including sex, ECOG PS, brain metastasis and treatment
for brain metastasis, were well balanced between the
crizotinib and ceritinib groups (Table 1); the age of the
patients receiving ceritinib was significantly older than
the patients receiving crizotinib (63 [56–69] vs. 54 [37–58];
P = 0.016) and the frequency of smoking history in
crizotinib group was lower than the ceritinib group (22.9%
vs. 38.5%; P = 0.298; Table 1). The median duration of
follow-up was 9.6 months for the crizotinib group and
36.0 months for the ceritinib group. At the time of analy-
ysis, 11 patients (31.4%) had discontinued treatment in the
crizotinib group and five patients (38.5%) had discontinued
treatment in the ceritinib group.

Treatmen t efficac y between crizotinib and
ceritinib
At the time of data cutoff, a total of 17 events of disease
progression or death had been noted (12 of 35 patients
[34.3%] in the crizotinib group and five of 13 patients
[38.5%] in the ceritinib group). The 18-month PFS rate
was significantly higher in the ceritinib group than in the
crizotinib group (87.5% [95% confidence interval,23 65.5 to
100.0] vs. 31.1% [95% CI, 15.8 to 46.4]); the hazard ratio
for disease progression or death was 0.27 (95% CI,
0.08–0.90; P = 0.033); and the median PFS with ceritinib

treatment was 32.3 months (95% CI, 19.6 to not

Table 1 Baseline characteristics of the study population

| Variables, n (%) | Total (n = 48) | Crizotinib (n = 35) | Ceritinib (n = 13) | P-value |
|------------------|---------------|-------------------|------------------|--------|
| Age, median (range), year | 60 (50–67) | 63 (56–69) | 54 (37–58) | 0.016 |
| Sex | | | | |
| Male | 24 (50.0) | 17 (48.6) | 7 (53.8) | 1.000 |
| Female | 24 (50.0) | 18 (51.4) | 6 (46.2) | |
| Smoking history | | | | |
| Smoker/ex-smoker | 13 (27.1) | 8 (22.9) | 5 (38.5) | 0.298 |
| Nonsmoker | 35 (82.9) | 27 (77.1) | 8 (61.5) | |
| ECOG PS | | | | |
| 0 or 1 | 46 (95.8) | 33 (94.3) | 13 (100.0) | 1.000 |
| 2 | 2 (4.2) | 2 (5.7) | 0 | |
| Staging | | | | |
| IIIC | 3 (6.3) | 3 (8.6) | 0 | 0.553 |
| IV | 45 (93.7) | 32 (91.4) | 13 (100.0) | |
| Histology | | | | |
| Adenocarcinoma | 48 (100.0) | 35 (100.0) | 13 (100.0) | 1.000 |
| Brain metastasis | | | | |
| Yes | 16 (33.3) | 12 (34.3) | 4 (30.8) | 1.000 |
| No | 32 (66.7) | 23 (65.7) | 9 (69.2) | |
| Treatment for brain metastasis (No./total No.) | | | | |
| WBRT | 7/8 (87.5) | 5/6 (83.3) | 2/2 (100) | 1.000 |
| SRS | 1/8 (12.5) | 1/6 (16.7) | 0 | |

ECOG PS, Eastern Cooperative Oncology Group performance status; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.
estimable), as compared with 12.9 months (95% CI, 10.6 to not estimable; log-rank test \( P = 0.020 \); Fig 1) with crizotinib treatment. The tumor burden was estimable for an objective response in 44 patients (31 with crizotinib and 13 with ceritinib), in which the CR, PR, SD and PD were 3.2%, 71.0%, 16.1% and 9.7% for the crizotinib group and 100% of PR in the ceritinib group (Fig 2); a better response rate was noted for the patients receiving ceritinib treatment (100.0% vs. 74.2%, \( P = 0.082 \); Table 2).

### Propensity score-matched cohort analysis

To address the confounding factors that can potentially affect the therapeutic efficacy between the two groups (i.e., mainly the age and smoking history), we performed propensity score matching analysis. After 1:2 matching according to the individual’s propensity score—one who belonged to the ceritinib group and two who belonged to the crizotinib group—patients with balanced clinical profiles were selected (Table 3). Among the propensity score-matched subpopulation, the median PFS of the ceritinib group remained longer than that of patients in the crizotinib group (45.0 months [95% CI, 19.6 to not estimable] vs. 11.5 months [95% CI, 6.6 to not estimable]; log-rank test \( P = 0.010 \); Fig 3); the 18-months PFS rate (85.7% [95% CI, 68.8 to 100.0] vs. 23.0% [95% CI, 3.6 to 42.4]) and the hazard ratio for disease progression or death, 0.18 (95% CI, 0.04–0.75; \( P = 0.018 \); Fig 3) were also significantly better for patients receiving ceritinib treatment.

### Pattern of disease progression between crizotinib and ceritinib

The pattern of post-treatment disease progression, either systemic or CNS progression, was analyzed in a fashion of competing risk based on a cumulative incidence rate. The rate of systemic progression was significantly lower over time with ceritinib treatment as compared to crizotinib treatment (cause-specific hazard ratio, 0.21; 95% CI 0.06–0.73; \( P = 0.014 \), Fig 4), where 2 (15.4%) patients in the ceritinib group and nine (25.7%) patients in the crizotinib group had an event of systemic progression. In addition, the rate of CNS progression was equivalent.
between ceritinib and crizotinib treatment (cause-specific hazard ratio, 1.27; 95% CI 0.33–4.94; P = 0.730, Fig 4).

Adverse events profile

The most commonly noted all grade adverse events in patients in the crizotinib group included nausea/poor appetite (seven patients; 20.0%), diarrhea (seven patients; 20.0%) and elevated AST/ALT (12 patients; 34.3%). In the ceritinib group, the most commonly noted all grade adverse events included diarrhea (seven patients; 53.8%), nausea/poor appetite (six patients; 46.2%) and vomiting (three patients; 23.1%; Table 4). Serious adverse events of grade 3–5 were noted in one (2.9%) patient showing elevated AST/ALT in the crizotinib group and three (23.1%) patients showing diarrhea in the ceritinib group. Dose reduction was needed in five out of 13 (38.5%) patients receiving ceritinib treatment.

Discussion

The present study retrospectively analyzed the treatment efficacy between crizotinib and ceritinib in the front-line

### Table 2 Objective response rate in the study population

| Variables, n (%) | Crizotinib (n = 31) | Ceritinib (n = 13) |
|------------------|---------------------|-------------------|
| Response         |                     |                   |
| No. of patients  | 23                  | 13                |
| % (95% CI)       | 74.2 (61.3–87.1)    | 100 (100–100)*    |
| Complete response, No. (%) | 1 (3.2) | 0 |
| Partial response, No. (%) | 22 (71.0) | 13 (100.0) |
| Stable disease, No. (%) | 5 (16.1) | 0 |
| Progression disease, No. (%) | 3 (9.7) | 0 |

*P = 0.082 for the comparison between ceritinib and crizotinib.

### Table 3 Characteristics of the propensity score-matched cohort

| Variables, n (%) | Total (n = 30) | Crizotinib (n = 18) | Ceritinib (n = 12) | P-value |
|------------------|----------------|---------------------|-------------------|---------|
| Age, median (range), year | 55 (45–62) | 56 (47–65) | 54 (42–59) | 0.472 |
| Sex              |               |                     |                   |         |
| Male             | 14 (46.7)     | 8 (44.4)            | 6 (50.0)          | 1.000   |
| Female           | 16 (53.3)     | 10 (55.6)           | 6 (50.0)          |         |
| Smoking history  |               |                     |                   |         |
| Smoker/ex-smoker | 11 (36.7)     | 6 (33.3)            | 5 (41.7)          | 0.712   |
| Nonsmoker        | 19 (63.3)     | 12 (66.7)           | 7 (58.3)          |         |
| ECOG PS          |               |                     |                   |         |
| 0 or 1           | 29 (96.7)     | 17 (94.4)           | 12 (100.0)        | 1.000   |
| 2                | 1 (3.3)       | 1 (5.6)             | 0                 |         |
| Staging          |               |                     |                   |         |
| IIIC              | 2 (6.7)       | 2 (11.1)            | 0                 | 0.503   |
| IV                | 28 (93.3)     | 16 (88.9)           | 12 (100.0)        |         |
| Histology        |               |                     |                   |         |
| Adenocarcinoma   | 30 (100.0)    | 18 (100.0)          | 12 (100.0)        | 1.000   |
| Brain metastasis |               |                     |                   |         |
| Yes              | 7 (23.3)      | 4 (22.2)            | 3 (25.0)          | 1.000   |
| No               | 23 (76.7)     | 14 (77.8)           | 9 (75.0)          |         |
| WBRT for brain metastasis | 4 (13.3) | 2 (11.1) | 2 (16.7) | 1.000 |

ECOG PS, Eastern Cooperative Oncology Group performance status; WBRT, whole-brain radiotherapy.
setting in a directly comparative manner. Patients who received ceritinib were associated with a significantly longer PFS than those who received crizotinib. Analysis of the pattern of disease progression between the two drugs showed that the higher treatment efficacy of ceritinib was mainly attributed to a significantly better control of systemic progression. Gastrointestinal symptoms and elevated liver function were the major adverse effects which accounted for the toxicity profiles of ceritinib and crizotinib treatment, respectively.

In the absence of a randomized head to head study comparing the efficacy between ceritinib and crizotinib in the first-line setting, previous studies addressed this by taking advantage of an indirect comparative approach using the patient cohort propensity score-matched from the ASCEND 4 and PROFILE 1014 trials.\(^1\)\(^1\) In this indirect comparison, ceritinib showed a significantly better treatment efficacy than crizotinib.\(^1\)\(^9\),\(^2\)\(^0\) Although this approach provided preliminary and insightful findings, it remained limited by the unadjustable bias inherent in each trial. The present study, otherwise analyzed in a manner of direct comparison, confirmed the finding noted in the previous indirect comparison.

An impressive efficacy of ceritinib with a PFS of 32.3 months was noted in the present study. This finding can be partly associated with the Asian ethnicity of our study population. A previous study of ceritinib treatment can be partly associated with the Asian ethnicity of our population. A previous study of ceritinib treatment can be partly associated with the Asian ethnicity of our population. A previous study of ceritinib treatment can be partly associated with the Asian ethnicity of our population.

Table 4 Treatment-related adverse events

|                | Crizotinib (n = 35) | Ceritinib (n = 13) |
|----------------|---------------------|--------------------|
| **Frequency n (%)** |                     |                    |
| Any grade       |                     |                    |
| Nausea/poor appetite | 7 (20.0) | 2 (15.4) |
| Diarrhea        | 7 (20.0) | 1 (2.9) |
| Vomiting        | 4 (11.4) | 1 (2.9) |
| Elevation of AST/ALT | 8 (22.9) | 5 (38.5) |
| Peripheral edema | 5 (14.3) | 0      |
| Blurred vision  | 2 (5.7)  | 0      |
| Dizziness       | 2 (5.7)  | 0      |

ALT, alanine transaminase; AST, aspartate transaminase.

Recently, the association between Asian ethnicity and efficacy of crizotinib treatment in the front-line setting has also been reported. Nishio et al. reported a PFS of 13.6 months and a 56% hazard reduction of disease progression and death for Asian patients in the PROFILE 1014 compared to a PFS of 9.6 months and a 48% hazard reduction for non-Asian patients in the same study.\(^2\)\(^4\) Taken together, the present study demonstrated a good efficacy of ceritinib and crizotinib treatment for Asian Taiwanese patients with ALK-positive NSCLC, with a superior efficacy in favor of ceritinib treatment.

The better therapeutic efficacy of ceritinib relative to crizotinib can be partly associated with a broader coverage of ceritinib treatment for multiple tumor clones, particularly for those with crizotinib-resistant ALK mutations. This can be understood by considering a similar scenario of the epidermal growth factor receptor gene (\(EGFR\)) mutated NSCLC treated by osimertinib relative to gefitinib/erlotinib in the front-line setting.\(^2\)\(^5\) Given osimertinib is a highly active agent for the treatment of gefitinib/erlotinib-resistant T790M tumor clone, the front-line administration of osimertinib allows the early eradication of T790M part within an \(EGFR\)-mutated tumor and thereby significantly improves tumor control relative to the front-line use of gefitinib/erlotinib. The successful suppression of the T790M tumor clone by the front-line use of osimertinib can also be suggested by the subsequent mechanisms of acquired resistance in which the T790M-mediated resistance can no longer be identified.\(^2\)\(^6\)

In line with the above mentioned context, an in vitro study has shown that ceritinib was highly active against tumor clones L1196M, G1269A, C1156Y and I1171T/N/S, which were the top four crizotinib-resistant mechanisms associated with the acquired ALK mutations.\(^2\)\(^7\)–\(^2\)\(^9\) Therefore, the early eradication of these tumor clones by the front-line administration of ceritinib may explain the better therapeutic efficacy, especially a favorable control of systemic progression, than the front-line use of crizotinib. Furthermore, it is of note that when the crizotinib-resistant tumor clones L1196M, G1269A, C1156Y and I1171T/N/S were treated with alectinib, they were not as sensitive as those treated by ceritinib in the in vitro study.\(^2\)\(^7\) Whether this could possibly be an explanation for the earlier finding of the ALEX trial in which the front-line use of alectinib, when compared to crizotinib, only showed an equivalent capacity for the control of systemic progression warrants further investigation.\(^2\)\(^0\)

Although the present study had its inherent limitations of being of a retrospective nature with a small sample size, it is of value given the lack of a direct head to head comparison between ceritinib and crizotinib. In addition, this analysis also suggested that the differential therapeutic efficacy between the two drugs when they were administered...
in the front-line to Asian patients should actually be massive, and therefore the difference could be easily discerned, even if the analysis only involved a small group of patients.

In conclusion, this study demonstrated that the administration of ceritinib in the front-line for the treatment of ALK-positive NSCLC had superior efficacy than crizotinib, in which a better control of systemic progression could be attributed to this finding.

Acknowledgments

We thank all the authors for their contribution. The study was supported by Chang Gung Medical Foundation grant number CMRP3G1672.

Disclosure

No authors report any conflict of interest.

References

1 Goldstraw P, Chansky K, Crowley J et al. The IASLC lung cancer staging project: Proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. J Thorac Oncol 2016; 11 (1): 39–51.
2 Kris MG, Johnson BE, Berry LD et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA 2014; 311 (19): 1998–2006.
3 Shaw AT, Kim DW, Nakagawa K et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013; 368 (25): 2385–94.
4 Solomon BJ, Mok T, Kim DW et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014; 371 (23): 2167–77.
5 Chen G, Chen X, Zhang Y et al. A large, single-center, real-world study of clinicopathological characteristics and treatment in advanced ALK-positive non-small-cell lung cancer. Cancer Med 2017; 6 (5): 953–61.
6 Gadgeel SM, Gandhi L, Riely GJ et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002[G]): Results from the dose-finding portion of a phase 1/2 study. Lancet Oncol 2014; 15 (10): 1119–28.
7 Poller B, Wagenaar E, Tang SC, Schinkel AH. Double-transduced MDCKII cells to study human P-glycoprotein (ABC1B) and breast cancer resistance protein (ABC2G) interplay in drug transport across the blood-brain barrier. Mol Pharm 2011; 8 (2): 571–82.
8 Tang SC, Nguyen LN, Sparidans RW, Wagenaar E, Beijnen JH, Schinkel AH. Increased oral availability and brain accumulation of the ALK inhibitor crizotinib by coadministration of the P-glycoprotein (ABC1B) and breast cancer resistance protein (ABCG2) inhibitor elacridar. Int J Cancer 2014; 134 (6): 1484–94.
9 Hida T, Nokihara H, Kondo M et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): An open-label, randomised phase 3 trial. Lancet 2017; 390 (10089): 29–39.
10 Peters S, Camidge DR, Shaw AT et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med 2017; 377 (9): 829–38.
11 Marsilje TH, Pei W, Chen B et al. Synthesis, structure–activity relationships, and in vivo efficacy of the novel potent and selective anaplastic lymphoma kinase (ALK) inhibitor 5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfanyl)phenyl)pyrimidine-2,4-diamine (LDK378) currently in phase 1 and phase 2 clinical trials. J Med Chem 2013; 56 (14): 5675–90.
12 Sakamoto H, Tsukaguchi T, Hiroshima S et al. CH5424802, a selective ALK inhibitor capable of blocking the resistant gatekeeper mutant. Cancer Cell 2011; 19 (5): 679–90.
13 Shaw AT, Kim TM, Crinò L et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): A randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2017; 18 (7): 874–86.
14 Soria JC, DSW T, Chiari R et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): A randomised, open-label, phase 3 study. Lancet 2017; 389 (10072): 917–29.
15 Friboulet L, Li N, Katayama R et al. The ALK inhibitor ceritinib overcomes crizotinib resistance in non-small cell lung cancer. Cancer Discov 2014; 4 (6): 662–73.
16 Kort A, Sparidans RW, Wagenaar E, Beijnen JH, Schinkel AH. Brain accumulation of the EML4-ALK inhibitor ceritinib is restricted by P-glycoprotein (P-GP/ABCB1) and breast cancer resistance protein (BCRP/ABCG2). Pharmacol Res 2013; 102: 200–7.
17 Kim DW, Mehra R, DSW T et al. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): Updated results from the multicentre, open-label, phase 1 trial. Lancet Oncol 2016; 17 (4): 452–63.
18 Crino L, Ahn MJ, De Marinis F et al. Multicenter phase II study of whole-body and intracranial activity with ceritinib in patients with ALK-rearranged non-small-cell lung cancer previously treated with chemotherapy and crizotinib: Results from ASCEND-2. J Clin Oncol 2016; 34 (24): 2866–73.
19 Li J, Knoll S, Bocharova I, Tang W, Signorovitch J. Comparative efficacy of first-line ceritinib and crizotinib in advanced or metastatic anaplastic lymphoma kinase-positive non-small cell lung cancer: An adjusted indirect comparison with external controls. Curr Med Res Opin 2018; 35(1): 105–111.
20 Tan DS, Araújo A, Zhang J et al. Comparative efficacy of ceritinib and crizotinib as initial ALK-targeted therapies in previously treated advanced NSCLC: An adjusted comparison with external controls. J Thorac Oncol 2016; 11 (9): 1550–7.
21 Satagopan JM, Ben-Porat L, Berwick M, Robson M, Kutler D, Auerbach AD. A note on competing risks in survival data analysis. *Br J Cancer* 2004; 91 (7): 1229–35.

22 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; 94: 496–509.

23 ADA’s advocacy stresses access to nutrition services in health care reform and children’s feeding programs. *J Am Diet Assoc* 1994; 94 (5): 496.

24 Nishio M, Kim DW, Wu YL et al. Crizotinib versus chemotherapy in Asian patients with ALK-positive advanced non-small cell lung cancer. *Cancer Res Treat* 2018; 50 (3): 691–700.

25 Soria JC, Ohe Y, Vansteenkiste J et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* 2018; 378 (2): 113–25.

26 Ramalingam SS, Cheng Y, Zhou C et al. Mechanisms of acquired resistance to first-line osimertinib: Preliminary data from the phase III FLAURA study. *Ann Oncol* 2018; 29 (Issue suppl_8): mdy424.063.

27 Gainor JF, Dardaei L, Yoda S et al. Molecular mechanisms of resistance to first- and second-generation ALK inhibitors in ALK-rearranged lung cancer. *Cancer Discov* 2016; 6 (10): 1118–33.

28 Lin YT, Yu CJ, Yang JC, Shih JY. Anaplastic lymphoma kinase (ALK) kinase domain mutation following ALK inhibitor(s) failure in advanced ALK positive non-small-cell lung cancer: Analysis and literature review. *Clin Lung Cancer* 2016; 17 (5): e77–94.

29 Katayama R, Lovly CM, Shaw AT. Therapeutic targeting of anaplastic lymphoma kinase in lung cancer: A paradigm for precision cancer medicine. *Clin Cancer Res* 2015; 21 (10): 2227–35.