Editorial

What can we learn from 3 phase III trials of ASCEND-4: ceritinib *vs*. platinum/pemetrexed with pemetrexed maintenance, PROFILE 1004: crizotinib *vs*. platinum/pemetrexed, and J-ALEX: alectinib *vs*. crizotinib?

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Comment on: Soria JC, Tan DS, 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;389:917-29.

Submitted Mar 24, 2017. Accepted for publication Mar 31, 2017.
doi: 10.21037/tcr.2017.04.20
View this article at: http://dx.doi.org/10.21037/tcr.2017.04.20

The echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) fusion gene is observed in 4–5% of non-small cell lung cancer (NSCLC) (1). The first-generation ALK-targeted tyrosine kinase inhibitor (TKI), crizotinib, showed significantly better objective responses rates (ORR) and longer progression free survival (PFS) than the standard platinum doublet chemotherapy in those patients (median PFS: 10.9 *vs*. 7.0 months, respectively; hazard ratio for progression or death with crizotinib: 0.45; ORR: 74% *vs*. 45%, respectively) (PROFILE 1014) (2). Now, ALK-TKI is considered as the first line standard treatment for patients with newly diagnosed advanced ALK-fusion gene positive NSCLC. Ceritinib is a next-generation, selective ALK inhibitor, approximately 28 to 39 times more potent than crizotinib against ALK-positive NSCLC cells. Moreover, ceritinib overcame several acquired crizotinib-resistant ALK mutations *in vitro* and *in vivo* (3).

In the recent article by Soria *et al*. (4), the efficacy, safety, and patient-reported outcomes of ceritinib versus platinum plus pemetrexed doublet chemotherapy with pemetrexed maintenance in chemotherapy naïve patients with advanced ALK-positive NSCLC were evaluated. This is a randomized, open-label, global, phase III study in which 134 institutions from 28 countries participated. All eligible patients were histologically or cytologically confirmed advanced or metastatic non-squamous NSCLC with ALK-rearrangement determined centrally by VENTANA anti-ALK (D5F3) immunohistochemistry assay. Treatment schedule was determined either daily ceritinib (750 mg) in the ceritinib arm or platinum (cisplatin: 75 mg/m^2 or carboplatin: AUC of 5–6) plus pemetrexed (500 mg/m^2) given every 21 days for four cycles followed by pemetrexed maintenance every 21 days if not progressive disease in the chemotherapy group. Primary endpoint was PFS. Median PFS was 16.6 months [95% confidence interval (CI): 12.6–27.2] in the ceritinib arm and 8.1 months (95% CI: 5.8–11.1) in the platinum/pemetrexed followed by pemetrexed arm [hazard ratio 0.55; 95% CI: 0.42–0.73; P<0.00001] (*Table 1*). Thus, ceritinib has been positioned as the first-line treatment in patients with advanced ALK-rearranged NSCLC. ASCEND-4 is the first study that a next-generation ALK-TKI demonstrated the superiority in PFS compared with platinum/pemetrexed doublet chemotherapy with pemetrexed maintenance.

After the PROFILE 1014 study started from January 2011, the regimen of cisplatin/pemetrexed followed by pemetrexed has been established as the standard of care for the non-squamous NSCLC patients with good performance status (PS) (5,6). With regard to this point, ASCEND-4 study represents a valid comparator against the use of chemotherapy in the real clinical setting in this era. As considered in the results of the PROFILE 1014 and the ASCEND-4 studies, we strongly confirmed ALK-TKI as the standard treatment for the first-line treatment against ALK-positive advanced NSCLC patients. In addition, ceritinib is only ALK-TKI, which was compared with current standard chemotherapy including pemetrexed maintenance.

Table 1 Comparison of patients characteristic, outcome, and adverse events in ASCEND-4, PROFILE1014, and J-ALEX.

Clinical trial	ALK inhibitor			Control		
	ASCEND-4	PROFILE1014	J-ALEX	ASCEND-4	PROFILE1014	J-ALEX
	Ceritinib	Crizotinib	Alectinib	Pt + PEM > PEM	Pt + PEM	Crizotinib
n (randomized cases)	189	172	103	187	171	104
PS (%) 0/1/2	37/57/7	94/6[‡]	52.4/45.6/1.9	37/56/7	95/5[‡]	46.2/51.9/1.9
Stage (%) III/IV/(rec)	5/95	2/98	2.9/73.8/(23.3)	3/97	2/98	2.9/72.1/(25.0)
Brain metastases (%)	31.0	26.0	13.6	33.0	27.0	27.9
PFS (m)	16.6	10.9	>20.3	8.1	7.0	10.2
HR (*vs*. control)	0.55	0.45	0.34			
PFS with BM (m)	13.5	9.0	NR	6.7	4.0	10.2
HR (*vs*. control)	0.58	0.40	0.09			
OS (m)	NR	NR	NR	26.2	NR	NR
HR (*vs*. control)	0.73	0.82	–			
Response rate (%)	72.5	74.0	76.0	26.7	45.0	71.0
Adverse events (%) (all grades)						
Diarrhea	85.0	61.0	8.7	11.0	13.0	73.1
Nausea	69.0	56.0	10.7	55.0	59.0	74.0
Vomiting	66.0	46.0	5.8	36.0	36.0	57.7
ALT increase	60.0	36.0[†]	8.7	22.0	13.0[†]	31.7
AST increase	53.0	36.0[†]	10.7	19.0	13.0[†]	30.8
IP	2.0	1.0	7.8	1.0	0.0	7.7

[†], elevated aminotransferase includes ALT and/or AST increase, [‡], indicated PS 0/1 and PS 2. PS, performance status; rec, recurrence post ope; BM, brain metastases; NR, not reached; PFS, progression free survival; OS, overall survival; HR, hazard ratio; IP, interstitial pneumonia.

Because of the high blood-brain barrier permeability of ceritinib (7), patients with asymptomatic or stable brain metastases were included and the assessment of the intracranial treatment responses was pre-planned in ASCEND-4. In the prior phase I study of ceritinib, the remarkable intracranial responses and duration of response in patients with chemotherapy naïve and post-treatment with ALK-TKI were observed (ORR: 63% and 36%; duration of response: 8.2 and 11.1 months, respectively) (8). Intracranial efficacy of first-line crizotinib (n=39) versus chemotherapy (n=40) in patients with treated brain metastases in PROFILE 1014 was extensively analyzed (9). ORR (77% *vs*. 28%; P<0.001), median PFS (9.0 *vs*. 4.0 months; P<0.001), and median intracranial intent-to treat (15.7 *vs*. 12.5 months; P=0.063) seem to be advantageous with crizotinib arm. Although crizotinib is efficacious in patients with brain metastases, newer ALK-TKIs including ceritinib, alectinib (10), brigatinib (11), and lorlatinib (12) seem to show better clinical response in the intracranial metastases (13). In ASCEND-4 study, overall intracranial response rate in patients with measurable baseline metastases 72.7% in the ceritinib arm and 27.3% in the platinum/pemetrexed with pemetrexed maintenance arm (hazard ratio: 0.58) (4). Although it remains unclear whether maintenance with pemetrexed was effective for suppression of brain metastasis compared to no maintenance, continuous treatment of pemetrexed inhibited brain metastasis after stereotactic irradiation (14). A randomized trial (alectinib *vs*. crizotinib) in Japanese ALK-TKI-naïve patients with ALK-positive NSCLC were recently reported to show longer PFS (>20.3 months) in alectinib arm than (10.2 months) in crizotinib arm (Table 1) (15).

Hazard ratio of PFS in patients with brain metastases is 0.09 although there was an imbalance between patient numbers with them (13.6% in alectinib arm and 27.9% in crizotinib arm) (*Table 1*). We learned that intracranial activity of ceritinib and crizotinib are better than that of chemotherapy. In addition, alectinib (and maybe ceritinib) shows better outcome regarding response and PFS than crizotinib in ALK-positive patients with brain metastases.

Most adverse events observed in ASDEND-4 study seemed mild and tolerable. Gastrointestinal toxicity including diarrhea, nausea, and vomiting in the ceritinib arm was higher than chemotherapy arm but most events were grade 1–2 (*Table 1*). Only 5% in ceritinib arm discontinued treatment due to adverse events. We may treat patients experiencing such toxicities with dose reduction (450 or 600 mg/day) or treatment interruption (16). Aminotransferases seemed to increase in ceritinib arm (ASCEND-4) and in crizotinib group (PROFILE 1014 and J-ALEX) (*Table 1*). Although incidence of interstitial pneumonia (around 8%) was high in both crizotinib and alectinib arms in J-ALEX study, drug-induced interstitial pneumonia often occurred in Japanese compared with other ethnicity (17). Thus, we cannot tell whether incidence of interstitial pneumonia by ceritinib was lower than that of crizotinib and alectinib. What we learned is that alectinib seems to have fewer adverse events compared with crizotinib and ceritinib.

The next-generation ALK-TKIs for the ALK-positive patients have been still performed in phase III settings: (I) NCT02075840 (ALEX), alectinib *vs.* crizotinib for systemic treatment-naïve patients in US; (II) NCT02373501 (ALTA-1L), brigatinib *vs.* crizotinib for patients who received up to 1 prior chemotherapy regimen and no previous TKIs including ALK-TKIs; (III) NCT02767804 (eXalt3), ensartinib *vs.* crizotinib for patients who received up to 1 prior chemotherapy regimen and no prior ALK-TKIs. Lorlatinib is now investigated in ALK-positive NSCLC patients who are treatment naïve or were treated with ALK-TKIs (NCT01970865, NCT02927340). Subsequently, the phase III study comparing lorlatinib with crizotinib in advanced ALK-positive patients without prior systemic NSCLC treatment just started on April 14, 2017 (NCT03052608). These results will help us to develop more efficient and less harmful treatment against ALK-positive NSCLC.

Long-term survival and ultimately cure without quality of life impairment in advanced ALK-positive NSCLC patients are our goals. Approaches to overcome the resistance using newer ALK-TKIs, cytotoxic agents, angiogenesis inhibitors, and immunocheckpoint inhibitors have also been performed in clinical trials (18). In the point of view of long-term overall survival, the benefit of experimental arms in ASCEND-4, PROFILE 1014, and J-ALEX studies has not been clarified. Thus, cytotoxic chemotherapy including pemetrexed and first-generation ALK-TKI such as crizotinib may be useful in first-line treatment because resistance mechanisms and therapeutic strategies overcoming resistance have been elucidated (19,20). Researchers are sincerely engaged in such translational and clinical studies, which will offer hope patients with the intractable disease (21-23).

Acknowledgments

Funding: This work was partly supported by JSPS KAKENHI Grant Number JP26830118 (NO).

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Shaohua Cui (Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China).

Conflicts of Interest: N Takigawa has received research funds and honoraria from Pfizer Inc., Japan, Chugai Pharmaceutical, Novartis Pharmaceutical, and Ili lilly Japan. N Ochi has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Ochi N, Takigawa N. What can we learn from 3 phase III trials of ASCEND-4: ceritinib *vs*. platinum/pemetrexed with pemetrexed maintenance, PROFILE 1004: crizotinib *vs*. platinum/pemetrexed, and J-ALEX: alectinib *vs*. crizotinib? Transl Cancer Res 2017;6(Suppl 3):S515-S518. doi: 10.21037/tcr.2017.04.20

