Editorial

Ceritinib: a new first-line therapy against ALK-rearranged lung cancer?

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About 20% of Caucasian non-small-cell lung cancer (NSCLC) patients (1), and 50% of Eastern Asian ones (2), are diagnosed with an oncogene-addicted disease, due to the presence of epidermal growth factor receptor (*EGFR*) activating mutations or anaplastic lymphoma kinase (*ALK*) and proto-oncogene tyrosine-protein kinase ROS (*ROS1*) rearrangements. These gene alterations identify patients who benefit from the use of correspondent inhibitors. On the other hand, in this era of personalized medicine, most NSCLC patients do not harbor such genetic alterations, thus chemotherapy represents the standard-of-care for first-line therapy (3,4).

ALK-rearrangements occur in 3–7% of NSCLC patients and seem to be associated with specific clinical characteristics including never or light smoking history, young age and adenocarcinoma histology with signet rings (1,2). Crizotinib, an oral small-molecule tyrosine kinase inhibitor (TKI) of *ALK*, *MET*, and *ROS1* kinases, is the standard-of-care for this subgroup of patients (3,4). However, most patients treated with crizotinib ultimately progress (5), with the central nervous system (CNS) being the common site of progression (6). To date, several small molecules are being developed as next-generation ALK-TKIs, such as ceritinib (LDK-378), alectinib (CH-5424802), brigatinib (AP26113), lorlatinib (PF-06463922), and ensartinib (X-396), showing significant activity in crizotinib-naive patients, as well as in patients experiencing progression on crizotinib (7). Most of these ALK-TKIs are able to cross the blood-brain barrier (BBB) with the potential increase of brain metastases control, too (7). Among these new inhibitors, ceritinib is in late stage of clinical development. Based on the first results coming from early phase trials (8-10), on April 29, 2014, and on June 04, 2015, the Food and Drug Administration (FDA) and the European Medicine Agency (EMA), respectively granted ceritinib accelerated approval for the treatment of patients with *ALK*-positive metastatic NSCLC who experience disease progression or who are intolerant to crizotinib.

Recently, the final results of the ASCEND-4 (11), open-label, phase III study, were published. In this trial, 376 untreated patients with advanced *ALK*-rearranged nonsquamous NSCLC were randomized to receive oral ceritinib, at the dose of 750 mg/day, or cisplatin 75 mg/m^2 or carboplatin at the area under the curve (AUC) 5–6 plus pemetrexed 500 mg/m^2, every 3 weeks, for four cycles followed by maintenance pemetrexed. Also patients with the presence of brain metastases were allowed to be enrolled. The primary endpoint was blinded independent review committee assessed progression-free survival (PFS). The median PFS was 16.6 months in the ceritinib group and 8.1 months in the chemotherapy group [hazard ratio (HR) 0.55; 95% confidence interval (CI): 0.42–0.73; P<0.00001]. The median PFS in patients without brain metastases (n=255) was 26.3 months in the ceritinib group versus 8.8 months in the chemotherapy group (HR 0.48; 95% CI: 0.33–0.69) while the median PFS in patients with brain metastases (n=121) was 10.7 months in the ceritinib group versus 6.7 months in the chemotherapy group (HR 0.70; 95% CI: 0.44–1.12). An overall response rate (ORR) as assessed by the blinded independent review committee was 72.5%

in the ceritinib group and 26.7% in the chemotherapy group. In patients with measurable brain metastases at baseline, the overall intracranial response was 72.7% in the ceritinib group and 27.3% in the chemotherapy group. The overall survival (OS) data were not mature with a median not reached in the ceritinib group and 26.2 months in the chemotherapy group (HR 0.73; 95% CI: 0.50–1.08; P=0.056). The median relative dose intensity was 78.4% for patients receiving ceritinib and 93.8–99.2% for each individual component in patients treated with chemotherapy. Drug-related toxicities were reported in 97% of patients treated with ceritinib and 89% of patients receiving chemotherapy. Grade ≥3 toxicities were reported in 65% and 40%, respectively, and the most common were an increase in alanine aminotransferase (30% versus 3%), aspartate aminotransferase (17% versus 2%) and gamma-glutamyltransferase (29% versus 2%) in the ceritinib group. In the chemotherapy group grade ≥3 hematologic toxicities, such as anemia (7% versus 2%) and neutropenia (11% versus 1%), were more frequent than in the ceritinib group. Patients discontinuing treatment due to adverse events were 5% in the ceritinib group and 11% in the chemotherapy group. Overall, general quality of life was in favor of ceritinib (11).

Based on these findings, ceritinib could be considered a further first-line therapeutic option in patients with ALK-rearranged NSCLC. The PROFILE 1014 study compared crizotinib, at the oral standard dose of 250 mg twice daily, to chemotherapy with cisplatin 75 mg/m² or carboplatin AUC 5–6 plus pemetrexed 500 mg/m², every 3 weeks, for six cycles. The primary endpoint was PFS assessed by independent radiologic review, which was 10.9 months for the crizotinib group versus 7.0 months for the chemotherapy group (HR 0.45; 95% CI: 0.35–0.60; P<0.001) (12).

Of course, the comparison between the ASCEND-4 (11) and PROFILE 1014 (12) trials is due (*Table 1*). The comparator of ceritinib and crizotinib, in both trials (11,12), was platinum/pemetrexed regimen (11,12). In the ASCEND-4 trial (11), platinum/pemetrexed was followed by pemetrexed maintenance. At the moment, this regimen is the standard-of-care for non-squamous NSCLC patients (3,4). This means that the chemotherapy regimen used in the ASCEND-4 trial was a robust comparator. In the PROFILE 1014 trial (12), the platinum/pemetrexed therapy was administered for a maximum of six cycles and then patients were followed-up until progression. At the time of the beginning of the PROFILE 1014 study, this chemotherapy regimen was the standard-of-care. Of interest is that the chemotherapy regimen administered in the ASCEND-4 trial showed a better PFS than the one used in the PROFILE 1014 study (11,12), while ceritinib showed a median PFS higher than the one reported with the crizotinib therapy. Surprisingly, ORR was higher for the chemotherapy regimen used in the PROFILE 1014 study than the one reported by the chemotherapy regimen employed in the ASCEND-4 study (11,12). Probably, the ORR of the chemotherapy regimen in the ASCEND-4 trial may be affected by the higher number of enrolled patients with brain metastases (32%). In the PROFILE 1014 study, of the 343 patients in the intent-to-treat population, 23% were affected by previously treated brain metastases. Median PFS was 9.0 months with crizotinib versus 4.0 months with chemotherapy (HR 0.40; 95% CI: 0.23–0.69). The global ORR was statistically significantly higher with crizotinib (77%) than with chemotherapy (28%; P<0.001) (6). In this subgroup of patients, the results were similar between the two trials but in the ASCEND-4 study (11), 16.7% of the enrolled patients did not receive any treatment for brain metastases and 8.2% with measurable baseline untreated brain metastases showed an intracranial ORR of 69.2% with ceritinib and 27.8% with chemotherapy (11). A preclinical rat model showed that ceritinib penetrates the BBB with a brain-to-blood exposure ratio of approximately 15%. This ceritinib efficacy was observed in patients previously treated with or without crizotinib (13). Overall, median PFS of patients with brain metastases and treated with ceritinib was 10.7 months, which is shorter than what reported in patients without brain metastases, which was 26.3 months. Moreover, brain was a common site of first progression on ceritinib both in patients with baseline brain metastases (48% of cases) and without brain metastases (30% of patients). Thus, brain metastases remained a big problem, especially in oncogene-addicted NSCLC due to the longer natural history of the disease, emphasizing the need for more effective strategies to manage CNS involvement.

Ceritinib, given at a starting dose of 750 mg/day, led to frequent toxicity, predominantly gastrointestinal (nausea, vomiting, and diarrhea) and raised liver function tests, necessitating dose interruptions or reductions in 80% of patients. These toxicities were more frequent than those reported with crizotinib in the PROFILE 1014 study (12), in which the most grade ≥3 toxicity were the aminotransferase levels elevations occurred in 14% of patients. Despite grade ≥3 toxicities occurred in 65% of patients treated with ceritinib, only 5% of cases led to its discontinuation (11). In

Table 1 Main characteristics of patients, outcomes and grade ≥3 toxicities for pivotal phase III trials of crizotinib and ceritinib in first-line treatment of ALK-rearranged NSCLC

Characteristics	PROFILE 1014 (12)		ASCEND-4 (11)	
	Crizotinib	Chemotherapy	Ceritinib	Chemotherapy
No. pts	172	171	189	187
Brain metastases (%)	26	27	31	33
ORR (%)	74	45	72.5	26.7
ORR brain metastases (%)	77	28	46.3*	21.2*
ORR untreated brain metastases (%)	NR	NR	46.9*	29.0*
PFS (months)	10.9	7.0	16.6	8.1
HR (95% CI); P value	0.45 (0.35–0.60); P<0.001		0.55 (0.42–0.73); P<0.00001	
PFS brain metastases (months)	9.0	4.0	10.7	6.7
HR (95% CI); P value	0.40 (0.23–0.69); P<0.001		0.70 (0.44–1.12); NR	
OS (months)	NM	NM	NM	26.2
1-year survival (%)	84	79	70.6°	58.2°
Diarrhea (%)	2	1	5	1
Nausea (%)	1	2	3	5
Vomiting (%)	2	3	5	6
Fatigue (%)	3	2	4	3
Elevated aminotransferases (%)	14	2	31	3
Gamma-glutamyltransferase (%)	NR	NR	29	3
Decreased appetite (%)	2	1	1	1
Neutropenia (%)	11	15	1	11

*, intracranial response; °, 2-year survival. ALK, anaplastic lymphoma kinase; NSCLC, non-small-cell lung cancer; No. pts, number of patients; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; NR, not reported; NM, not mature.

fact, the ceritinib dose modifications and use of supportive medications led to the optimal management of these toxicities. In this view, a phase I study to assess the systemic exposure, efficacy, and safety of ceritinib at the dose of 450 or 600 mg taken with a low-fat meal as compared with ceritinib at the standard dose of 750 mg taken in the fasted state is ongoing. The primary outcome of this study is to evaluate the plasma concentration of the different doses of ceritinib with the main secondary endpoints being safety profile and ORR (14).

It is important to stress that all the comparisons made between the ASCEND-4 and PROFILE 1014 trials should be considered with the caveats of cross-trial comparisons due to the lack of head-to-head trials involving crizotinib and ceritinib. Unfortunately, ceritinib was compared with chemotherapy and not with crizotinib which is the standard-of-care for ALK-rearranged lung cancer patients. However, the ASCEND-4 trial started when crizotinib was not considered the first-line choice yet. The ASCEND-4 trial gives us a new weapon for first-line therapy in this subgroup of patients, and drug choice for each patient should be based on the balance between efficacy and toxicity. To date, the J-ALEX trial is the only study comparing head-to-head two ALK-TKIs, specifically crizotinib versus alectinib, suggesting that efficacy with new generation ALK-TKIs might be superior to crizotinib, particularly in patients with brain metastases (15). There are further ongoing or planned phase III first-line trials comparing head-to-

head new generation ALK-TKIs which can produce new important information for the treatment of this subgroup of NSCLC patients. Considering the results reported by the ASCEND-4 trial showing a very impressive median PFS, ceritinib is most probably the best comparator for future head-to-head trials. The availability of several ALK-TKIs arises the question of which might be the optimal sequential approach to these patients, many of whom have diseases which are still ALK-dependent even beyond progression on first-line ALK-TKIs. In the next future, for ALK-addicted NSCLC patients, trials investigating different sequential strategic approaches with different ALK-TKIs are warranted.

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Footnote

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References

1. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA 2014;311:1998-2006.
2. Shi Y, Au JS, Thongprasert S, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol 2014;9:154-62.
3. Masters GA, Temin S, Azzoli CG, et al. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015;33:3488-515.
4. Novello S, Barlesi F, Califano R, et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v1-v27.
5. Katayama R, Shaw AT, Khan TM, et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung Cancers. Sci Transl Med 2012;4:120ra17.
6. Solomon BJ, Cappuzzo F, Felip E, et al. Intracranial Efficacy of Crizotinib Versus Chemotherapy in Patients With Advanced ALK-Positive Non-Small-Cell Lung Cancer: Results From PROFILE 1014. J Clin Oncol 2016;34:2858-65.
7. Rossi A. Alectinib for ALK-positive non-small-cell lung cancer. Expert Rev Clin Pharmacol 2016;9:1005-13.
8. Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med 2014;370:1189-97.
9. Kim DW, Mehra R, Tan DS, 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;17:452-63.
10. Nishio M, Murakami H, Horiike A, et al. Phase I Study of Ceritinib (LDK378) in Japanese Patients with Advanced, Anaplastic Lymphoma Kinase-Rearranged Non-Small-Cell Lung Cancer or Other Tumors. J Thorac Oncol 2015;10:1058-66.
11. 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.
12. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014;371:2167-77.
13. Toyokawa G, Seto T, Takenoyama M, et al. Insights into brain metastasis in patients with ALK+ lung cancer:

is the brain truly a sanctuary? Cancer Metastasis Rev 2015;34:797-805.
14. Pharmacokinetic and safety study of lower doses of ceritinib taken with a low-fat meal versus 750 mg of ceritinib in the fasted state in adult patients with (ALK-positive) metastatic non-small cell lung cancer (NSCLC). (NCT02299505) (This study is currently recruiting participants). Available online: https://www.cancer.gov (accessed on: March 18, 2017).
15. Nokihara H, Hida T, Kondo M, et al. Alectinib (ALC) versus crizotinib (CRZ) in ALK-inhibitor naive ALK-positive non-small cell lung cancer (ALK+ NSCLC): Primary results from the J-ALEX study. J Clin Oncol 2016;34:abstr 9008.

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