Since the discovery of anaplastic lymphoma kinase (ALK)-rearrangement in non-small lung cancer (NSCLC) in 2007, there are now four approved ALK tyrosine kinase inhibitors (TKIs) (crizotinib, ceritinib, alectinib, brigatinib) in the US with the most recent one (brigatinib) approved in the US on April 28, 2017 (1). Crizotinib, the first ALK TKI introduced clinically, demonstrated statistically significant improved progression-free survival over platinum-based chemotherapy in two randomized phase 3 trials (PROFILE 1014 and 1029) in advanced treatment-naïve ALK-rearranged NSCLC (2,3). However, resistance will inevitably develop in majority of patients within 12 months from initiation of treatment. Ceritinib is the first next-generation ALK TKI to be approved by the US Food and Drug Administration (FDA) based on the significant overall response rate and duration of response from the phase 1 ASCEND-1 trial (4,5). Updated clinical efficacy from ASCEND-1 indicated ALK-rearranged NSCLC patients who are refractory to prior ALK TKI achieved a median PFS of 6.9 months when treated with ceritinib (6). Ceritinib is a more potent ALK inhibitor with an inhibitory concentration at 50% (IC\textsubscript{50}) of 0.2 nM in pure enzymatic inhibitory assay (7) and able to inhibit some of the acquired resistance ALK mutations to crizotinib (8). Thus expectation was high that ceritinib could extend the survival benefit of crizotinib in ALK-rearranged NSCLC patients. Pooled analysis of several institutions that participated in the ASCEND-1 indicated sequential use of crizotinib then ceritinib (with or without intervening chemotherapy) could provide median overall survival to 49.4 (9) months higher than a previous retrospective analysis of median OS of 29.6 months with just continuation of crizotinib beyond progression (10). The median PFS of ceritinib in this pooled analysis was 7.8 months. In the follow up phase 2 study on ALK-rearranged NSCLC patients who had disease progression on chemotherapy and crizotinib (ASCEND-2), ceritinib achieved a median PFS of 5.7 months (by investigators assessment) or 7.2 months [by blinded independent reviewed committee (BIRC)] (11). ASCEND-5 was designed as one of the two pivotal trials comparing ceritinib to chemotherapy. Specifically ASCEND-5 randomized ALK-rearranged NSCLC patients who had progressed on chemotherapy and crizotinib (ASCEND-2), ceritinib achieved a median PFS of 5.4 months compared to 1.6 months for single chemotherapy as determined by independent review committee [hazard ratio (HR) =0.49; P<0.0001] (12). Ceritinib also achieved an ORR of 45% versus 8% for single agent chemotherapy. Furthermore, adverse events suspected to be treatment-related were reported in 96% (110/115) in the ceritinib group. The most frequent reported any-grade adverse events were diarrhea (63%), nausea (61%), vomiting (48%), increased ALT concentration (42%), and decreased appetite (33%). The most frequent grade 3–4 adverse event in the ceritinib group were increased ALT (21%) concentration, increased γ-GT
concentration (21%), and increased AST concentration (14%). The efficacy of ceritinib observed in this phase 3 study (ASCEND-5) was numerically inferior to that reported in phase 2 (ASCEND-2) data in a similar patient group who had previously received crizotinib and chemotherapy. Despite the similar number of patients treated with ceritinib and a higher proportion of patients with brain metastasis (71% vs. 57%) and heavily pretreated (three or more prior lines of treatment: 56% vs. 11%) in the ASCEND-2 than ASCEND-5, the median PFS of ceritinib dropped from independent review committee determined 7.2 to 5.4 months. Thus while ASCEND-5 was a positive trial, the actual median PFS achieved had progressively shorter from ASCEND-1 to ASCEND-2 to ASCEND-5. All the while, two other next generation ALK TKI have reported phase 2 clinical efficacy data in crizotinib-refractory or crizotinib-intolerant ALK-rearranged NSCLC patients with brigatinib achieving a median PFS of 12.9 months in the ALTA trial at the time of its publication (1). Contemporaneously, ASCEND-4 which compared ceritinib to platinum/pemetrexed doublet chemotherapy in treatment-naive ALK-rearranged NSCLC patients (13) and ALEX which compared alectinib to crizotinib in treatment-naive ALK-rearranged NSCLC (14). While both trials are positive in favor of ceritinib and alectinib respectively, ceritinib achieved a median PFS of 16.8 months (13) while alectinib achieved a median PFS of 25.7 months (by independent review committee) (14).

Additionally, progression in the central nervous system (CNS) is common in ALK-rearranged NSCLC patient receiving crizotinib. The cumulative incidence of CNS relapse approached 42% at 12 months and ~50% at 18 months based on the results of ALEX in which patients undergo regularly scheduled imaging of the brain regardless of the presence or absence of brain metastasis at the time of enrollment (14). Thus the ability to delay or prevent progression in the CNS will be an important asset of next generation ALK inhibitor. In ASCEND-5, ceritinib was associated with statically significant higher intracranial response than chemotherapy with 35% of patients had an overall intracranial response in the ceritinib versus 5% in the chemotherapy group. The median PFS of patients with brain metastasis at enrollment treated with ceritinib was 4.4 months compared to 1.4 months with chemotherapy (HR =0.5) in ASCEND-5. On the other hand, the median PFS of patients without brain metastasis at enrollment treated with ceritinib 6.9 vs. 2.4 months with chemotherapy (HR =0.45). In comparison to alectinib and brigatinib albeit from single arm phase 2, alectinib and brigatinib seemed to have numerical superior disease control in the CNS when compared to ceritinib (1) although no similarly designed phase 3 randomized trials like ASCEND-5 comparing alectinib or brigatinib to single agent chemotherapy have been conducted. Finally, in the ALEX study, alectinib achieved excellent PFS in ALK-rearranged NSCLC patients with or without baseline CNS metastasis (14) while the median PFS achieved by ceritinib in ASCEND-4 in ALK-rearranged NSCLC patients with pre-existing brain metastases were much shorter (10.7 months) than ALK-rearranged NSCLC patients without brain metastasis at enrollment (26.3 months) (13).

Poor tolerability of approved dose of ceritinib of 750 mg once daily has always hindered the wide use of ceritinib. The median relative dose intensity of ceritinib was 82% based on a median duration of treatment of approximately 7.1 months in ASCEND-5, while the relative median dose intensity of ceritinib in ASCEND-4 was 78.4% based on a median duration of treatment of 15.5 months (13). In comparison, the mean dose intensity of alectinib was much higher at 95.6% from the ALEX study with a longer median duration of treatment of 17.9 months (14). Recently study from ASCEND-8 indicating the pharmacokinetic (PK) level of ceritinib is similar between 750 mg taken on an empty stomach and 450 mg taken with food with slightly less adverse events (15). However, the efficacy of ceritinib at 450 mg with food cannot be assumed to be equivalent to the efficacy of ceritinib at the approved 750 mg once daily dose (with which ASCEND-2, -4, and -5 were conducted) without any data from randomized trials.

In conclusion while ASCEND-5 established ceritinib as a superior treatment option than single chemotherapy post-crizotinib progression, the rapid development and approval of other next generation ALK inhibitor has diluted the importance of this finding. With the looming approval and wide adaptation of alectinib as first-line treatment of advanced treatment-naive ALK-rearranged NSCLC patients based on the ALEX trial and supported by the J-ALEX trial (16), the role of ceritinib post-alectinib has never been explored. Lorlatinib, another next generation ALK inhibitor has presented clinical meaningful activity in ALK-rearranged NSCLC patient who had disease progression on 1 prior ALK inhibitor regardless of the specific ALK inhibitor and has received “breakthrough therapy designation” (BTD) from the US FDA (17). Thus in our opinion, the future role of ceritinib in the treatment of ALK-rearranged NSCLC as a second-line therapy post-
crizotinib failure is narrow and limited given the many next generation ALK inhibitors available and likely adoption of alectinib as the front-line treatment of ALK-rearranged NSCLC leaving the role of ceritinib post-alectinib undefined.

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Footnote
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