The ALK fusion oncogene was first identified in non-small cell lung cancer (NSCLC) in 2007 (1). It has been identified in approximately 3–7% of NSCLC cases, and more commonly in younger patients, and non- or light smokers. The central nervous system (CNS) is the most common site of disease progression, with many incidences of brain metastases diagnosed at disease onset. In the last 10 years, the discovery of ALK rearrangements has led to the rapid emergence of various ALK inhibitors, many developed in response to ALK resistance mutations that develop to crizotinib and to improve responses in the CNS.

Crizotinib is a first-generation oral small molecule tyrosine kinase inhibitor (TKI) of ALK, MET and ROS1 kinases. PROFILE 1014 is a phase III trial which established crizotinib’s role as first-line treatment in patients with advanced ALK rearrangements when compared to platinum-doublet chemotherapy. The median progression-free survival (PFS) favored the crizotinib arm at 10.9 months compared to 7.0 months in the chemotherapy arm (HR =0.45; 95% CI, 0.35–0.60; P<0.001). An overall survival difference between the two arms was not appreciated, likely due to the ability for patients who progressed on the chemotherapy arm to crossover to the crizotinib arm (2). These results contributed to the establishment of crizotinib as standard first-line treatment in advanced ALK-positive patients.

Many resistance mechanisms to crizotinib have been identified. Secondary mutations in the ALK gene such as the gatekeeper L1196M mutation, L1152R, C1156Y, S1206Y, G1202R, G1269A, and several others, have been reported in approximately 22% to 36% of patients (3-6). In addition, ALK amplifications and activation of bypass pathways such as EGFR, IGFR-1R, and KIT amplification have also been found to contribute to resistance (6,7). More potent ALK inhibitors compared to crizotinib have been developed which notably result in response rates of >50% or greater following crizotinib resistance despite multiple resistance mechanisms, which speaks to the dependency of ALK-rearranged tumors on ALK signaling even after resistance to crizotinib develops.

Ceritinib is a second-generation oral small molecule TKI which inhibits ALK, IGF-1 and ROS1 kinases. PROFILE 1014 is a phase III trial which established ceritinib’s role as first-line treatment in patients with advanced ALK rearrangements when compared to platinum-doublet chemotherapy. The median progression-free survival (PFS) favored the ceritinib arm at 10.9 months compared to 7.0 months in the chemotherapy arm (HR =0.45; 95% CI, 0.35–0.60; P<0.001). An overall survival difference between the two arms was not appreciated, likely due to the ability for patients who progressed on the chemotherapy arm to crossover to the ceritinib arm (2). These results contributed to the establishment of ceritinib as standard first-line treatment in advanced ALK-positive patients.

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Ceritinib is a second-generation oral small molecule TKI which inhibits ALK, IGF-1 and ROS1 and was found to be 20 times more potent than crizotinib in preclinical studies, particularly in response to crizotinib-resistant mutations. Results from the phase I trial, ASCEND-1, led to the accelerated FDA approval of ceritinib in 2014 for ALK-positive patients with crizotinib-resistance, or who were unable to tolerate crizotinib (8). Recently, results from the ASCEND-4 trial led to the approval of ceritinib in previously untreated metastatic ALK-positive patients. In that study, 376 patients were randomized to receive either ceritinib or platinum-pemetrexed doublet chemotherapy. The median PFS was doubled with ceritinib at 16.6 vs. 8.1 months with chemotherapy (HR =0.55; 95% CI, 0.42–0.73; P<0.0001). Response rate was increased as well as a longer median duration of response with ceritinib.
was observed (9). Given these results, ceritinib was FDA-approved this year for use in the first-line setting in metastatic ALK-positive patients (10).

Recently reported results from the phase III ALEX study is expected to dramatically alter the long-standing use of standard first-line crizotinib. In this study, the second-generation ALK inhibitor alectinib was compared to crizotinib in the first-line setting for advanced ALK-positive NSCLC. The median PFS at 25.7 months with alectinib was found to be superior to crizotinib at 10.4 months (HR =0.50; 95% CI, 0.36–0.70; P<0.001). In addition, only 12% of patients in the alectinib group had CNS progression, compared to 45% of patients in the crizotinib group (cause-specific HR =0.16; 95% CI, 0.1–0.28; P<0.001) (11). These results are likely to soon bring alectinib to the forefront in the sequencing of ALK inhibitors for these patients, and if so, will further change the field’s current thoughts on the optimal sequencing of other ALK inhibitors.

For patients previously treated with crizotinib, there are several contenders amongst the next-generation ALK inhibitors. Shaw and colleagues report the results from ASCEND-5, the phase III trial of ceritinib versus chemotherapy in pre-treated ALK-positive patients (12). In this randomized, open-label trial, 231 patients were enrolled. All patients were previously treated with at least one chemotherapy regimen and crizotinib for at least 21 days with documented disease progression. The patients were evenly randomized to receive either ceritinib or chemotherapy (investigator’s choice of either pemetrexed or docetaxel). In the ceritinib arm, more patients were white (70% vs. 59%) and in the chemotherapy arm, more patients were ex-smokers (44% vs. 34%). Otherwise, patient characteristics between the two groups were similar. Treatment in both groups was continued until disease progression. Eighty-two (71%) patients in the ceritinib group and 108 patients (93%) in the chemotherapy group discontinued therapy. Patients in the chemotherapy group were permitted to cross-over to the ceritinib group upon progression.

The median PFS was 5.4 months (95% CI, 4.1–6.9) in the ceritinib group compared to 1.6 months [1.4–2.8 months; HR =0.49 (95% CI, 0.36–0.67); P<0.0001] in the chemotherapy group. Median duration of response in the ceritinib group was 6.9 months (95% CI, 5.4–8.9) and in the chemotherapy group was 8.3 months (95% CI, 3.5 to not estimable), however it is noted that there were few responders in the chemotherapy group leading to a wide confidence interval. Overall survival data was not yet mature at the time of the primary analysis.

More than half of the patients (58%) had brain metastases at baseline, with 66 patients in the ceritinib group and 67 patients in the chemotherapy group. Of these patients, median PFS for the ceritinib group was 4.4 months (95% CI, 3.4–6.2) compared to 1.5 months (95% CI 1.3–1.8) in the chemotherapy group. Patients who had not previously received radiotherapy for brain metastases or had progression of intracranial disease were analyzed and found that 6 of 17 (35%) patients in the ceritinib group (95% CI, 14.2–61.7) compared to 1 of 20 (5%) in the chemotherapy group (95% CI, 0.1–24.9) had an overall intracranial response.

The majority (96%) of patients in the ceritinib group experienced treatment-related adverse events, compared to 76% in the chemotherapy group. In the ceritinib arm, common adverse events of any-grade included diarrhea, nausea, and vomiting and were also the most frequently reported. In the chemotherapy group, common adverse events of any-grade included fatigue, nausea and alopecia. In the ceritinib group, 80% of patients required a dose adjustment or interruption or delay due to an adverse event, compared to 38% in the chemotherapy group. There were a slightly higher number of patients who discontinued treatment with chemotherapy (7%) compared to ceritinib (5%), both mostly due to treatment-related adverse events. Two deaths occurred in the ceritinib group related to an adverse event (cerebrovascular accident, respiratory failure), although neither were deemed to be treatment-related. Compared to ASCEND-1 and ASCEND-2, no new safety signals were found.

The authors do note that in comparison to the PROFILE 1007 study comparing second-line crizotinib or chemotherapy, the ASCEND-5 results demonstrated a shorter PFS in the chemotherapy arm of 1.6 months compared to 3.0 months in the PROFILE 1007 study. They attributed this difference to ASCEND-5 including a more heavily pretreated patient population who had also been previously exposed to crizotinib. In addition, a higher percentage of patients (57%) in the PROFILE 1007 trial compared to ASCEND-5 (34%) received pemetrexed in the chemotherapy arm, which has been demonstrated in prior studies to have an increased response in ALK-positive NSCLC. A greater percentage of patients also had baseline brain metastases in the ASCEND-5 trial.

The results from this trial support the prior approval for ceritinib in the second-line setting, however, in the current and dynamic landscape of ALK-positive NSCLC, where...
ceritinib may ultimately be indicated is unclear. In this trial, patients experienced more adverse events with ceritinib compared to chemotherapy, a consequence which cannot be ignored in this era of targeted therapy. Although there were few treatment-related discontinuations with ceritinib compared to chemotherapy, many more patients on ceritinib required dose adjustments, interruptions or delays. Approval of additional next-generation ALK inhibitors, alectinib and brigatinib, also in the second-line setting with better side effect profiles also makes ceritinib a less attractive choice in this setting.

Results from the North American NP28761 and the Global NP28673 Phase II trials led to the FDA-approval of alectinib in patients who progressed or were intolerant of crizotinib (13,14). Pooled analysis of these two trials demonstrated that in patients previously treated with both crizotinib and chemotherapy, ORR was 49.3% (95% CI, 41.0–57.7%) compared to 58.5% (95% CI, 42.1–73.7%) in chemotherapy-naive patients. Although the chemotherapy-naive patients had a slightly increased response rate, the median duration of response was longer in chemotherapy-exposed patients at 14.9 months (95% CI, 11.0–21.9) compared to 11.2 months (95% CI, 8.0 to not estimable) in the chemotherapy-naive.

Alectinib was overall well-tolerated in both trials. Common adverse events included constipation, fatigue, peripheral edema, myalgia, nausea, cough, and headache and most were grade 1 or 2. About a third of all patients had dose modifications or interruptions due to adverse events, and 6% of patients discontinued treatment (15).

The ALTA trial provided the data leading to brigatinib approval. In this phase II trial, patients treated with prior chemotherapy and crizotinib were randomized to one of two dosing regimens for brigatinib, 90 mg vs. 180 mg daily. ORR in the 90 mg arm was 45% and in the 180 mg arm was 54%. The higher dose of 180 mg had an increased median PFS at 12.9 months compared to 9.2 months at 90 mg, as well as an increased intracranial ORR (67% vs. 42%). Common adverse events included nausea, diarrhea, headache and cough (16).

With the plethora of next-generation ALK inhibitor options approved in the second-line setting, the optimal choice is undetermined as none were compared head-to-head, and patient characteristics between trials vary. Currently, re-biopsy at the time of disease progression is not mandated to document ALK resistance mechanisms as in the case of the T790M mutation EGFR-mutated NSCLC. The various known resistance profiles for each second-generation ALK inhibitor, however, suggests a potential benefit to choosing an agent based on a patient’s known resistance mutation. For example, the G1202R resistance mutation is not responsive to ceritinib or alectinib, but has been reported to be responsive to brigatinib and lorlatinib (16,17). Consideration of serial biopsies should be considered at each incidence of disease progression to determine the next optimal ALK inhibitor.

Results from ASCEND-5 are not convincing enough to advocate the preferred use of ceritinib in the second-line setting. With its toxicities, the utility and benefit of ceritinib may only be realized if our choice of ALK inhibitor becomes more focused on an individual’s resistance profile. Specifically, the V1180L and I11171T mutations were identified as alectinib-resistant ALK mutations, but were sensitive to ceritinib (18).

On this 10-year anniversary since ALK was first identified as a potential target in NSCLC, there is much to be excited and hopeful for given the rapid strides that have been made thus far. Additional next-generation ALK inhibitors such as lorlatinib and ensartinib are already in phase III trials and newer agents are entering clinical trials—these will further add to the discussion of how to best sequence these agents to combat various resistance mechanisms. Too often our challenges as oncologists result from a lack of treatment options, but for our patients with advanced ALK-positive NSCLC, we find ourselves in the unusual position of having many options but without a clear choice at disease progression. Continued research on these resistance mechanisms and refining our ability to deliver precision medicine to our patients, however, may lead us to realize that not just one universal optimal sequence of ALK inhibitors will exist, but an optimal sequence can be tailored around each individual with ALK-positive NSCLC.

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Footnote

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