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Lung Cancer (HA Wakelee, Section Editor)

Sequencing of ALK Inhibitors in ALK+ Non-Small Cell Lung Cancer

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Opinion statement

Major therapeutic advances have occurred over the last several years in the management of advanced ALK+ NSCLC patients. Crizotinib was the first agent approved for the management of ALK+ NSCLC patients after it demonstrated significantly greater clinical benefit compared to chemotherapy. Several next generation ALK inhibitors have demonstrated clinical benefit in patients with crizotinib refractory NSCLC patients including in the CNS. Based on available data, therapy with a next generation ALK inhibitor can be initiated following therapy with crizotinib without any assessment of the molecular mechanisms of resistance. The appropriate therapy for patients with progressive disease following two ALK inhibitors is not well defined. In patients with an ALK-resistant mutation in their tumor, an ALK inhibitor with activity against the mutation would be the most appropriate therapy. In others, chemotherapy and PD-1 directed agents can be considered. Clinical data suggests that ALK+ patients are less likely to benefit from PD-1 directed agents and therefore chemotherapy should be considered prior to these agents for the management of ALK+ NSCLC patients.

Introduction

In the recent years, genetic alterations that are responsible for initiation and maintenance of the malignant phenotype have been identified in several cancers including non-small cell lung cancer (NSCLC). Drugs targeting these alterations, often called "driver" genetic alterations, can provide significant clinical benefit. One of the genetically defined subsets of NSCLC is the ALK (anaplastic lymphoma kinase) positive subset. In recent years, major therapeutic advances have occurred in this subset of NSCLC.

In 2007, Soda and colleagues identified in the adenocarcinoma of the lung of a 62-year-old male patient, a small inversion in the small arm of chromosome 2 resulting in an oncogenic fusion gene comprising of

portions of EML4 (echinoderm microtubule-associated protein-like 4) and portions of ALK gene [1••]. It is now recognized that there are several different variants of EML4-ALK translocation dependent on variations in the length of the EML4 gene involved in the fusion gene. In addition, in less than 5% of ALK+ NSCLCs, the fusion partner is other than EML4 and includes genes such as KIF5B and TFG [2].

Data from several patient series has shown that ALK+ NSCLC comprises about 4% of NSCLCs. The demographics of these patients are distinct with the median age of about 55 years and about 70% of the patients are never smokers. Almost always the histology is adenocarcinoma. The incidence of ALK+ NSCLC is similar across all regions of the world and is similar among men and women [2].

Activity of crizotinib in ALK+ NSCLC

Advances in the management of ALK+ NSCLC started with the recognition that crizotinib can provide clinical benefit in these patients. Activity of crizotinib was first identified in a phase I trial PROFILE1001 [3]. After clinical activity was identified in ALK+ NSCLC patients during the dose escalation phase of the trial, the study was modified to include an expansion cohort of ALK+ NSCLC patients [4]. In this expansion cohort, 149 NSCLC patients whose tumors were determined to be ALK+ based on the break apart FISH (fluorescence in situ hybridization) test were enrolled. The response rate in this cohort of patients was 61% and median progression free survival was 9.7 months. The most common toxicities with crizotinib were visual disturbances, nausea, vomiting, constipation, and diarrhea. The most common grade 3 or higher toxicities were liver enzyme elevations and neutropenia.

These results were confirmed in a phase III trial, PROFILE 1007 that randomized previously treated ALK+ NSCLC patients to crizotinib or standard second line chemotherapy of docetaxel or pemetrexed [5]. The median progression free survival (PFS) with crizotinib in these patients was 7.7 months versus 3 months among patients who received chemotherapy (hazard ratio 0.49; 95% CI 0.37–0.64, $p < 0.001$). The response rate with crizotinib at 65% was significantly higher than the 20% response rate with chemotherapy ($p < 0.001$). No new adverse effects were observed with crizotinib. Overall survival was no different, possibly due to the planned crossover to crizotinib, which occurred in 62% of the patients randomized to chemotherapy. Analysis of patient-reported outcomes demonstrated significantly greater reduction in symptoms including cough, dyspnea, and fatigue with crizotinib. In addition, there was a significant increase in global quality of life with crizotinib compared to chemotherapy ($p < 0.001$).

Crizotinib was also assessed as front line therapy in PROFILE 1014 [6••]. Patients were randomized to either crizotinib or 6 cycles of chemotherapy with pemetrexed and cisplatin or carboplatin. Maintenance pemetrexed was not the accepted standard of care at the time the study was designed. There was a planned crossover to crizotinib at disease progression for patients who received chemotherapy. The median PFS was significantly longer with crizotinib at 10.9 months compared to chemotherapy at 7 months (HR 0.45, $p < 0.001$). The response rate with crizotinib was also greater at 74% with crizotinib and 45% with chemotherapy. The probability of 1 year survival was 84% with crizotinib and 79% with chemotherapy. No unexpected adverse events were

observed with crizotinib. The patient reported outcomes demonstrated a significant improvement in global quality of life with crizotinib compared to chemotherapy ($p < 0.001$). In addition, there was a greater decline in symptoms of dyspnea, cough, and pain in different parts of the body with crizotinib.

The cumulative evidence from all the trials demonstrates that crizotinib provides greater clinical benefit than chemotherapy in patients with advanced ALK+ NSCLC. The benefit does appear to be greater when it is the first systemic drug as suggested by the response rate of 74% and median progression free survival of 10.9 months observed in PROFILE 1014 compared to the response rate of 65% and median progression free survival of 7.7 months, observed in PROFILE 1007. Based on these data, crizotinib is approved and is recommended for use as front line therapy in patients with advanced ALK+ NSCLC.

Recently, Yoshida, et al. published on the variability of crizotinib activity in tumors with different ALK variants [7]. The variants are defined by the size of the EML4 gene involved in the ALK fusion gene. In a relatively small series, they demonstrated that the median PFS was 11 months in variant 1, the most common variant, but was only 4.2 months in patients with tumors that were non-variant 1. These data suggest that better understanding of the biological factors that can influence the activity of crizotinib may allow a more personalized approach to ALK+ NSCLC patients.

Resistance to crizotinib

Almost all patients treated with crizotinib eventually develop tumor progression. Broadly, there are three major mechanisms of resistance to targeted drugs: genetic alteration in the target, activation of bypass tracks or phenotypic change in the tumor such as development of epithelial mesenchymal transition, and finally, limited penetration to "sanctuary" sites such as the CNS (central nervous system) [8••]. All three mechanisms of resistance have been identified in patients treated with crizotinib [9, 10]. Target alteration, either as ALK mutations or ALK amplification, occurs in about 30% of the tumors resistant to crizotinib. Activation of bypass pathways including MET amplification, EGFR mutation, and Kras mutations have also been identified in crizotinib refractory tumors. In a significant proportion of patients, the exact mechanism of resistance is unknown.

CNS is a common site of progression in crizotinib-treated patients, with 70% of the patients experiencing progression in the CNS [11••]. Progression in the CNS maybe a result of limited penetrance of crizotinib through the blood brain barrier making CNS a sanctuary site and also could be due to acquired resistance to crizotinib [12].

Next generation ALK inhibitors

Since tumor progression is almost a certainty with crizotinib, there is clearly a need for potent inhibitors of ALK that can overcome resistance to crizotinib including in the CNS. Several agents have been evaluated in patients with crizotinib refractory NSCLC, two of which are currently approved in the USA, ceritinib and alectinib, and a third agent brigatinib has received break through designation by the US FDA. In pre-clinical models, each of these agents has

Table 1. Next generation ALK inhibitors in crizotinib refractory NSCLC

Design/assessment	Ceritinib[15] *N* = 163 Phase I/II investigator/BIRC	Alectinib[16] *N* = 138 Phase 2 BIRC	Brigatinib[17] *N* = 110 Phase 2 investigator
PS 2	12%	9%	8%
Brain Mets	60%	61%	67%
Previous Rx	56% (≥3 prior)	80% (≥2 prior)	74% (≥2 prior)
ORR	56% (49–64)	50% (41–59)	54% (43–65)
CNS response	36%* *N* = 28	57% *N* = 35	67% *N* = 12
Median PFS	6.9 m (5.6–8.7)	8.9 (5.6–11.3)	15.6 (11.1-NR)

demonstrated more potent inhibition of ALK than crizotinib [13, 14]. The response rates with these agents, in patients with crizotinib refractory disease, are between 50 and 55% and the median progression free survival is from 6 to 15 months [15–17] (Table 1). In addition, each of these agents demonstrated activity in the CNS. Few other next generation ALK inhibitors are in development. Ensartinib is another next generation ALK inhibitors that has shown promising activity in ALK positive NSCLC patients including in the CNS. Activity was not only observed with this drug in crizotinib-resistant patients but also in patients who had received ≥2 ALK inhibitors [18].

Recently, the results of the ASCEND-5 trial were presented. In this trial, patients who had previously received chemotherapy and crizotinib were randomized to ceritinib or chemotherapy (pemetrexed or docetaxel). The results demonstrated a significant improvement in PFS, with a median PFS of 5.4 months compared to 1.6 months with chemotherapy (HR 0.49, $p < 0.001$) [19]. These data clearly demonstrate that a next generation ALK inhibitor is the preferred treatment in patients previously treated with crizotinib.

As with crizotinib, eventually, patients also develop tumor progression on the next generation of ALK inhibitors. Gainor et al. reported on molecular analysis of tumors of 46 patients with disease progression on ceritinib (23 patients), alectinib (17 patients), and brigatinib (6 patients) [14]. All of these patients had received prior crizotinib. They identified ALK mutations in 56% of the patients with the most common ALK mutation being G1202R. A minority of patients had more than one ALK mutation. Thus, patients following disease progression on next generation of ALK inhibitors are more likely to have ALK mutations in their tumors than patients who develop disease progression on crizotinib. It is unclear if similar molecular mechanisms of resistance will be observed in patients who receive the next generation agents as front line therapy.

There is very limited data regarding treatment of patients previously treated with ≥2 different ALK inhibitors. Solomon et al. presented data on the activity of lorlatinib in a dose escalation study [20]. In this study, lorlatinib demonstrated a response of 42% with a median PFS of 9.2 months among 26 patients who had received ≥2 prior ALK inhibitors. Activity was also observed in the CNS in these patients (Table 2). In pre-clinical models, Gainor et al. evaluated the

Table 2. Activity of lorlatinib in patients who have received ≥2 ALK inhibitors [20]

	***N* = 26 patients**
Complete response	2 (8%)
Partial response	9 (35%)
Overall response rate	11 (42%) (95% CI, 23–63%)
Median PFS	9.2 months (95% CI, 1.5 NR)

activity of lorlatinib in tumors resistant to ceritinib. They found that lorlatinib demonstrated anti-tumor activity only in tumors with ALK resistance mutations and lacked activity in ceritinib-resistant tumors without ALK mutations [14]. Thus, it is possible that in the future, the decision to utilize a third ALK inhibitor for the treatment of ALK+ NSCLC may be guided by the presence or absence of ALK-resistant mutations in the progressing tumor.

The adverse event profiles of these agents are somewhat different. Gastrointestinal adverse events, particularly nausea/vomiting and diarrhea are common with ceritinib. In a small minority of patients treated with brigatinib, particularly at doses above 90 mg, pulmonary adverse events within the first week of treatment were observed. Muscle aches have been observed with alectinib. Some patients treated with lorlatinib, particularly at doses above 100 mg daily, have experienced cognitive effects including memory deficits and patients also can experience hypercholesterolemia. Knowledge of unique adverse effects with each of these agents is essential to make the proper choice of drug for a particular patient.

Next generation of ALK inhibitors as initial therapy

Pre-clinical models have shown that next generation ALK inhibitors are more potent inhibitors of ALK than crizotinib. With the recognition that the next generation of ALK inhibitors are more potent at inhibiting ALK and that they have activity in the CNS, there is an interest in evaluating these drugs as the first ALK inhibitor in patients with advanced ALK+ NSCLC.

Recently, Nokihara et al. presented the results of JALEX, a phase III trial conducted in Japan, randomizing advanced ALK+ NSCLC patients to alectinib or crizotinib [21••]. At the second planned interim analysis, the study demonstrated that the progression free survival, the primary end point of the study, was significantly improved with alectinib as compared to crizotinib (HR0.34, $p < 0.0001$). At a median follow up of about 12 months, the median progression free survival (PFS) was 10.2 months with crizotinib and the median progression survival was not reached in patients on alectinib. In subgroup analysis, the hazard ratio for PFS in patients with brain metastases at baseline was 0.08. However, the study did not stratify patients based on presence of brain metastases and there were only 43 patients with brain metastases enrolled on the trial. Alectinib appeared to be better tolerated than crizotinib with serious adverse events occurring in 14.6% of alectinib and 26% of crizotinib

patients. Adverse event related drug discontinuation occurred in 9% of alectinib patients and 20% of crizotinib patients.

There is hesitation on the part of some experts to change the standard of care based on the results of this study, since this study was conducted only in Japan and the results of the global study ALEX comparing the same two drugs are not yet available. In addition, data regarding ALK-directed therapeutic options in patients who have received alectinib is limited. Therefore, there is a concern that starting a patient on alectinib may limit therapeutic options over the course of the patient's cancer. Available data with lorlatinib and availability of other next generation ALK inhibitors could minimize this concern.

Recently, the results of ASCEND-4 trial that randomized ALK+ treatment naïve patients to ceritinib or chemotherapy were presented [22]. With a median follow up of 19.7 months, the progression free survival was significantly improved with ceritinib compared to chemotherapy with a hazard ratio of 0.55 (95% CI 0.42–0.73), $p < 0.001$. The median PFS with ceritinib was 16.6 versus 8.1 months for patients on chemotherapy. Despite an intracranial response rate of 72%, the PFS benefit with ceritinib appeared to be somewhat less in patients with brain metastases with a HR of 0.70 (95%CI 0.44–1.12) and a median PFS of 10.7 versus 6.7 months in patients on chemotherapy. Ceritinib also improved quality of life and lung cancer symptom scores compared to chemotherapy. The rate of study drug related AEs occurred in 16% of patients who received ceritinib and 15.4% of patients who received chemotherapy. Study drug related AEs led to drug discontinuation in 5.3% of ceritinib patients and 11.4% of chemotherapy patients. The median dose intensity of ceritinib was 78.4% (range 30.4–100). These results suggest that ceritinib could be another option for the front line management of ALK+ NSCLC patients.

Data with other ALK drugs as the first ALK inhibitor are limited, though ongoing and planned trials will define their activity as first ALK inhibitor. One measure of success with next generation of ALK inhibitors as first ALK inhibitors is whether the clinical benefit obtained by starting with next generation of ALK inhibitors provides longer clinical benefit than starting with crizotinib followed by a next generation drug. Though such data are not available to date, inferences can be drawn from available trial results. In the JALEX trial, the median survival with alectinib as first ALK inhibitor was greater than 20 months. The median survival with crizotinib in PROFILE 1014 was 11 months, and the median survival of alectinib in crizotinib refractory patients is 9 months. Thus, JALEX data suggests that alectinib as the first ALK inhibitor may provide greater benefit than crizotinib followed by alectinib. It remains to be seen whether further follow up of JALEX trial and the expected results of ALEX trial confirm this observation.

Non-ALK-directed agents

Many ALK+ NSCLC patients during their course of illness require therapy with other agents. Pre-clinical data suggests that lorlatinib is not likely to be beneficial in tumors resistant to ceritinib that do not have ALK mutations [14]. Therefore, non-ALK-directed therapy is a consideration following treatment with at least two ALK inhibitors. Cytotoxic chemotherapy is the common non-ALK-directed therapy utilized. Data on efficacy of platinum-based doublet

chemotherapy following treatment with two ALK inhibitors is not available. In EGFR mutation, positive patients, combination of cisplatin and pemetrexed, demonstrated a response rate of 33% and a median PFS of 5.4 months following therapy with an EGFR-TKI [23]. It is possible that in ALK+ NSCLC patients, chemotherapy results in similar outcomes.

With the approval of agents targeting PD-L1-PD-1 interaction, these immune checkpoint inhibitors are also an option in the management of ALK+ NSCLC patients. Recently, Gainor et al. published the results of a retrospective analysis of the use of these agents in 28 patients with EGFR mutation (n = 22 patients) or ALK translocations (n = 6 patients) [24]. Of these patients, only one EGFR mutation positive patient had tumor response to a PD-1 directed agent. This response rate was far lower than the response rate of 23% among 30 patients, treated at the same institution, who were EGFR and ALK wild type or ALK unknown. These data are consistent with previous observations that these agents are less likely to be beneficial in patients who are never smokers and patients with EGFR mutation positive tumors [25]. It is suggested that tumor response with these agents is likely in patients with tumors that have high mutational load [26]. Mutational load of NSCLCs in patients who are never smokers is lower than lung cancers in smokers and therefore these never smokers are less likely to have tumor response to PD-1 directed agents.

Gainor et al. also analyzed PD-L1 expression by immunohistochemistry in a separate cohort of EGFR mutation and ALK+ NSCLCs. Among 27 ALK+ NSCLCs, PD-L expression at any level was observed in 63% of the tumors and high (≥50% of the cells) PD-L1 expression was observed in 26% of the tumors. Results of several trials suggest that these agents are much less likely to provide clinical benefit in patients with tumors that are PD-L1 low or no expression [25, 27, 28]. In addition, in a randomized trial pembrolizumab demonstrated greater PFS and survival than platinum-based chemotherapy in advanced NSCLC patients with high PD-L1 expressing tumors [29]. Though PD-L1 expression is an imperfect marker to predict for benefit from PD-1 directed agents as suggested by a response rate of only 35–45% among patients with high PD-L1 tumors and a low but not zero response rate among patients with tumors that have low or no PD-L1 expression; PD-L1 expression maybe particularly helpful in guiding use of these agents in ALK+ NSCLC patients. Thus, PD-1 directed agents could be considered after disease progression on two ALK inhibitors in ALK+ NSCLC patients if their tumors are PD-L1 high and later in the course of their disease if the tumors are PD-L1 low or zero.

Management of oligometastatic disease

A proportion of NSCLC patients at presentation have metastases limited in number and sites or develop progression of disease after initial therapy only in few sites of metastases. Clinical data has suggested that local ablative therapy to the limited number of metastases in addition to systemic therapy may provide longer disease control [30, 31]. A retrospective analysis of 65 ALK+ (n = 38) or EGFR mutation positive (n = 27) NSCLC patients from a single institution demonstrated that progression free survival in patients who developed progression in ≤4 sites had a median PFS of 6 months after local ablative therapy to the sites of progression and continuation of the targeted therapy [32].

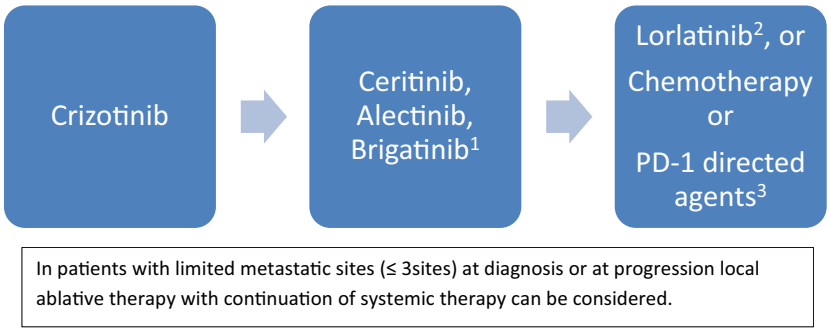

Fig. 1. Current treatment schema for management of ALK+ NSCLC patients.

Recently, Gomez et al. published the results of a phase II trial of advanced NSCLC patients with three or fewer metastatic sites at the start of initial therapy, who were randomized to local ablative therapy in addition to systemic therapy or not [33]. Of the 49 patients on the study, only two patients had ALK+ NSCLC. The study showed a significantly longer median PFS of 11.9 months in patients who received ablative therapy versus median PFS of 3.9 months in patients who did not (HR 0.35, $p = 0.0054$). These data are consistent with prior observations of longer disease control among patients with oligometastatic disease who receive local therapy. Though the study is small and only had two ALK+ NSCLC patients, these observations could be extended to the management of ALK+ NSCLC patients.

Despite the availability of several new agents for the treatment of ALK+ NSCLC, none of these agents cure patients with advanced disease. Therefore, local ablative therapy should be judiciously considered in patients with oligometastases both after response to initial therapy as well as in patients who develop disease progression in limited sites. For patients with oligoprogression, a personal preference is to consider local ablative therapy to

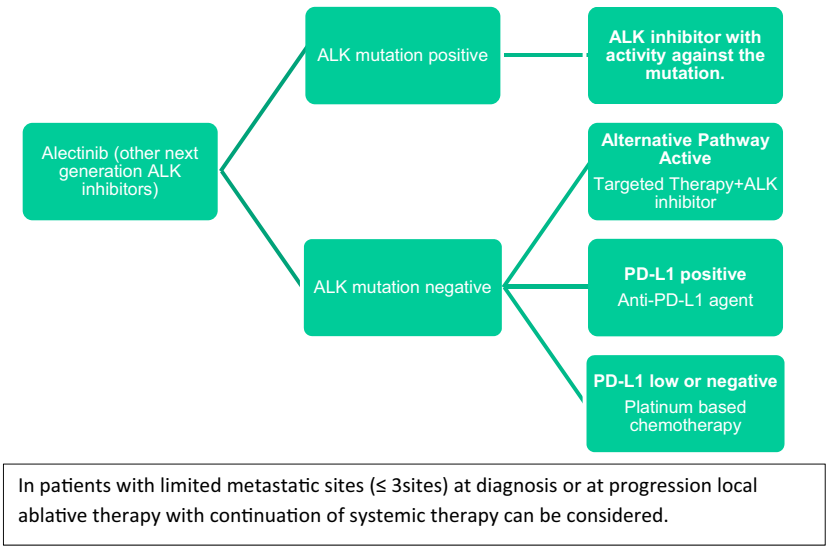

Fig. 2. Future treatment schema for ALK+ NSCLC patients.

the sites of progression and continuation of the systemic agent in patients who had prolonged disease control with the systemic agent prior to development of progression. However, if the patient has developed progression after only a short time on the systemic agent, switching systemic therapy is the suggested option.

Sequencing of therapy for ALK+ NSCLC patients

Since the discovery of ALK translocation as a driver genetic alteration in some NSCLCs, several therapeutic advances based on a greater understanding of the tumor biology have occurred in this subset of NSCLC. Data from the Lung Cancer Mutation Consortium showed that the median survival of ALK positive patients in their series was 4.25 years (2.92-NA) [34]. It is likely that the median survival with the currently available agents is even superior. It is therefore imperative that proper choices are made in the management of these patients.

A schema based on currently approved and available treatments (also expected to be approved in the near future) is presented in Fig. 1. A likely treatment schema in the near future is presented in Fig. 2. Presently, crizotinib is the only approved agent for the front line management of advanced ALK+ NSCLC patients. In patients who have crizotinib refractory NSCLC, next generation of ALK inhibitors have demonstrated clinical benefit and therefore should be the preferred agents. In patients who have developed disease progression after two ALK inhibitors, lorlatinib if available should be a consideration, especially if an ALK mutation is identified in the patient's tumor. Another option for patients who have received two prior ALK inhibitors is platinum-pemetrexed combination chemotherapy. Patients whose tumors are known to have high PD-L1 expression could be considered for a PD-1 directed agent before considering chemotherapy. However, if the PD-L1 expression is low or negative, chemotherapy should be considered prior to PD-1 directed agents.

Based on the results of the JALEX and the ASCEND-4 trials and other ongoing or recently completed trials, it is likely that in the future, next generation ALK inhibitors will be preferred for the management of ALK+ NSCLC patients. Subsequent therapy in patients who have received a next generation ALK inhibitor as front line therapy is likely to be guided by molecular analysis of the progressing tumor. Thus, an ALK inhibitor is likely to be the next agent used if an ALK mutation, sensitive to the next agent, is identified as the mechanism of resistance. In addition, presence of an activated alternative pathway may form the basis of adding a targeted agent to the ALK inhibitor to reverse resistance [34]. Otherwise, patients may undergo systemic chemotherapy or treatment with PD-1 directed agents if the tumor has high PD-L1 expression.

Future directions

It is expected that one of the next generation of ALK inhibitors will be used as the first ALK inhibitor for the management of advanced ALK+ NSCLC patients. It is unclear if the mechanisms of resistance to these agents as the first ALK inhibitor will be similar to the mechanisms of resistance identified when they are used after crizotinib. In addition, it is not clear if a specific sequence of therapeutic agents influences the biology of the cancer and therefore the clinical

course of the patient. Therefore, there is a need to conduct a trial that specifically assess the sequence of therapeutic agents defined by the molecular characteristics of the patient's tumor that is likely to provide sustained clinical benefit.

Despite the availability of several ALK inhibitors, further significant advances in clinical outcomes are unlikely to occur with single-agent therapy. Combination therapy that combines targeted agent against relevant pathways such as Src to an ALK inhibitor may provide greater clinical benefit [35]. Another approach is to add a PD-1 directed agent to an ALK inhibitor. Such an approach has led to unacceptable adverse events in EGFR mutation positive NSCLC patients [36]. It remains to be seen if similar issues with toxicity are also observed when these agents are combined with ALK inhibitors.

Summary

Over the last 9 years, data generated in ALK+ NSCLC patients has shown that ALK inhibitor can provide significant benefit in these patients and that a more potent ALK inhibitor can provide even greater benefit and can overcome tumor resistance to first generation ALK inhibitor. With the availability of several agents, it is has become extremely important that sequencing therapy based on molecular characteristics of the tumor with the goal of maximizing clinical benefit is the primary focus in the management of advanced ALK+ NSCLC patients.

Compliance with Ethical Standards

Conflict of Interest

Shirish M. Gadgeel has received compensation from Roche/Genentech, Pfizer, Bristol-Myers Squibb, ARIAD, and Boehringer Ingelheim for serving on advisory boards, and from AstraZeneca for both serving on an advisory board and as a guest speaker.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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