Recent advances in ALK-POSITIVE NSCLC

A HemOnc Today Special Report

Alice T. Shaw, MD, PhD, discusses future of ALK inhibitors
Combination therapy, first-line approvals on the horizon

Brigatinib safe, effective in crizotinib-resistant disease
Agent demonstrates increased CNS activity at higher dose

Alectinib improves PFS, CNS response in previously treated patients
ALUR trial confirms agent as standard of care in ALK-positive NSCLC

David Ross Camidge, MD, PhD, reviews potential of lorlatinib
Agent appears promising after treatment with crizotinib

This HemOnc Today supplement is produced by SLACK Incorporated.
New class of inhibitors change treatment paradigm in ALK-positive non-small cell lung cancer

The development of ALK inhibitors, which began with the approval of crizotinib in 2011, has produced a ‘phenomenal’ shift in the prognosis for patients with ALK-positive non-small cell lung cancer. Average OS is now approaching 5 years. Alectinib ( Alecensa, Genentech) has replaced crizotinib (Xalkori; Pfizer, EMD Serono) as first-line therapy, although ongoing research indicates that brigatinib (Alunbrig, Takeda) and lorlatinib (PF-06463922, Pfizer) may have even greater activity in the first-line setting. Additional areas of focus include combating resistance to the ALK inhibitors and treating brain metastases, both of which are common in most patients with ALK-positive NSCLC.

This supplement, brought to you by the publishers of HemOnc Today, highlights recent developments in ALK-positive NSCLC and features commentaries from prominent physicians about the direction of future research.

For additional headlines, visit Healio.com/Hematology-Oncology. – The Publishers of HemOnc Today

WEB WATCH

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Research highlights treatment trends, modifiable risk factors in lung cancer

Recent lung cancer research examines the role of new therapies in treating brain metastases and the link between physical activity and development of the disease. To read more about lung cancer, including the full articles summarized below, please visit Healio.com/Hematology-Oncology.

Role of targeted therapies, immunotherapy in brain metastases must be confirmed

The treatment of brain metastases, which affect as many as 65% of patients with lung cancer, may be redefined with systemic therapies, including immunotherapy and targeted agents, but more clinical trials with larger numbers of patients are needed to enhance existing data.

Lifetime physical inactivity increases risk for lung cancer

Lifetime physical inactivity appears to be significantly associated with risk for lung cancer in both patients who had never smoked and non-smokers. Physical inactivity also appeared associated with lung cancer mortality, which remained significant among non-smokers.
**For patients with ALK+ metastatic NSCLC who have progressed on or are intolerant to crizotinib**

**Think One Step Ahead With ALUNBRIG® (brigatinib)**

**Robust Overall Efficacy**

<table>
<thead>
<tr>
<th>ALTA Efficacy Results</th>
<th>IRC Assessment*</th>
<th>Investigator Assessment*</th>
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<tbody>
<tr>
<td>90 mg once daily (n=112)</td>
<td>58% (95% CI)</td>
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<tr>
<td>90 mg once daily + 90 mg once daily (n=110)</td>
<td>50% (95% CI)</td>
<td>48% (95% CI)</td>
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<tr>
<td>Overall Response Rate, (95% CI)</td>
<td>48% (39-58)</td>
<td>45% (35-54)</td>
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<tr>
<td>Complete Response, (n, %)</td>
<td>4 (3.6)</td>
<td>5 (4.5)</td>
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<tr>
<td>Partial Response, (n, %)</td>
<td>50 (45)</td>
<td>53 (48)</td>
</tr>
<tr>
<td>Duration of Response, Median in Months (95% CI)</td>
<td>13.8 (7-4E)</td>
<td>13.8 (9.3-NE)</td>
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</tbody>
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**Meaningful CNS Efficacy**

<table>
<thead>
<tr>
<th>Intracranial Objective Response in Brain Metastases† in ALTA</th>
<th>IRC Assessment*</th>
<th>Follow-Up Data (18-Month Median Follow-Up)††</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 mg once daily (n=26)</td>
<td>42% (23-63)</td>
<td>67% (41-87)</td>
</tr>
<tr>
<td>90 mg once daily + 90 mg once daily (n=18)</td>
<td>50% (30-70)</td>
<td>67% (41-87)</td>
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**Intracranial Overall Response Rate, (95% CI) | Complete Response, (n, %) | Partial Response, (n, %) | Duration of Intracranial Response, Median (months) (range)
<table>
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<tbody>
<tr>
<td>42% (23-63)</td>
<td>2 (7.7)</td>
<td>9 (39)</td>
<td>NE (1.9-9.2)</td>
</tr>
<tr>
<td>50% (30-70)</td>
<td>0</td>
<td>12 (67)</td>
<td>NR (3.7-NE)</td>
</tr>
</tbody>
</table>

*90 mg once daily with a 1-day hold in the 90 mg once daily.

**Systematic follow-up data (18-month median follow-up) is consistent with 6-month median follow-up.**

**ALTA Study Design:** The safety and efficacy of ALUNBRIG® were evaluated in a global, two-arm, open-label, multicenter trial. The trial consisted of 222 adult patients with locally advanced or metastatic ALK+ NSCLC who had progressed on crizotinib. Patients were randomized to receive the recommended dosing regimen of 90 mg of ALUNBRIG orally once daily with a 1-day hold in the 90 mg once daily (n=118, 18 with measurable brain metastases), or 90 mg of ALUNBRIG daily with measurable brain metastases. The primary efficacy outcome measure was confirmed objective response rate (dPR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by an Independent Review Committee (IRC). Additional efficacy outcome measures included investigator-assessed dPR, duration of response (DOR), intracranial DOR, and intracranial DCR.

**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS (continued)**

**Hypertension:** In ALTA, hypertension was reported in 11% of patients in the 90 mg group who received ALUNBRIG and 21% of patients in the 90-180 mg group. Grade 3 hypotension occurred in 5.9% of patients overall. Monitor blood pressure after 2 weeks and at least monthly thereafter during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 hypertension despite optimal antihypertensive therapy. Upon resolution or improvement to Grade 1 or 2, resume ALUNBRIG at a reduced dose. Consider permanent discontinuation of treatment with ALUNBRIG for Grade 4 hypertension or recurrence of Grade 5 hypertension. Use caution when administering ALUNBRIG in combination with antihypertensive agents that cause bradycardia.

**Bradycardia:** Bradycardia can occur with ALUNBRIG. In ALTA, heart rates less than 50 beats per minute (bpm) occurred in 5.7% of patients in the 90 mg group and 7.6% of patients in the 90-180 mg group. Bradycardia was observed in 10.9% (95% CI) patient in the drug arm. Monitor heart rate and blood pressure during treatment with ALUNBRIG. Patient monitors more frequently if concomitant use of drug known to cause bradycardia cannot be avoided for symptomatic bradycardia. Withhold ALUNBRIG and review concomitant medications for those known to cause bradycardia. However, use ALUNBRIG if bradycardia is identified and discontinue or dose adjusted, resume ALUNBRIG at the same dose following resolution of symptomatic bradycardia; otherwise, reduce the dose of ALUNBRIG following resolution of symptomatic bradycardia. Discontinue ALUNBRIG for life-threatening bradycardia if no contributing concomitant medication is identified.

**Visual Acuity:** In ALTA, adverse reactions leading to visual disturbance including blurred vision, diplopia, and reduced visual acuity were reported in 7.3% of patients treated with ALUNBRIG in the 90 mg group and 10% of patients in the 90-180 mg group. Grade 3 visual acuity disturbance or visual acuity disturbances leading to visual disturbance were reported in 3% of patients in the 90 mg group and 3% of patients in the 90-180 mg group. Advise patients to report any visual symptoms. Withholds ALUNBRIG and obtain an ophthalmologic examination in patients with new or worsening visual symptoms of Grade 2 or greater severity. Upon recovery of Grade 2 or Grade 3 visual disturbances to Grade 1 severity or baseline, resume ALUNBRIG at a reduced dose. Permanently discontinue treatment with ALUNBRIG for Grade 4 visual disturbances.

**Patient Information:** Visit ALUNBRIG.com to learn more. USE IN SPECIFIC POPULATIONS

**Pregnancy:** ALUNBRIG can cause fetal harm. Advise females of reproductive potential to use effective non-hormonal contraception during treatment and for at least 4 months after the last dose. Advise males with female partners of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 3 months after the last dose.

**Breastfeeding:** ALUNBRIG can cause fetal harm. Advise females of reproductive potential to use effective non-hormonal contraception during treatment and for at least 4 months after the last dose.

**Lactation:** There are no data regarding the secretion of brigatinib in human milk or its effects on the breastfed infant or milk production. Because of the potential adverse reactions in breastfed infants, advise lactating females not to breastfeed during treatment with ALUNBRIG.

**Females and Males of Reproductive Potential:**

**Contraception:** Advise females of reproductive potential to use effective non-hormonal contraception during treatment and for at least 4 months after the final dose. Advise males with female partners of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 3 months after the final dose.

**Embryo-Fetal Toxicity:** Inform females of reproductive potential that ALUNBRIG can cause fetal harm. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months after the last dose.

**CYP3A Substrates:** CYP3A inhibitors can result in decreased concentrations and loss of efficacy of CYP3A substrates. At the 8-month median follow-up, among the 23 patients who exhibited an intracranial response, 78% of patients in the 90–mg and 68% of patients in the 90–180 mg arm maintained a response for at least 4 months.

**Drugs that may increase bradycardia:**• CYP3A inhibitors: Avoid concomitant use of ALUNBRIG with strong CYP3A inhibitors. Avoid grapefruit or grapefruit juice as it may also increase plasma concentrations of brigatinib. If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce the dose of ALUNBRIG.

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**IMPORTANT SAFETY INFORMATION (continued)**

**ADVERSE REACTIONS**

Serious adverse reactions occurred in 38% of patients in the 90 mg group and 40% of patients in the 90-180 mg group. The most common serious adverse reactions were pneumonitis (5.4% overall, 3.7% in the 90 mg group, and 7.3% in the 90–180 mg group). Fatal adverse reactions occurred in 3.7% of patients and consisted of pneumonitis (2 patients), sudden death, dyspnea, respiratory failure, pulmonary embolism, cerebral infarcts and unruptured or ruptured aneurysm (1 patient each).

The most common adverse reactions (≥25%) in the 90 mg group were nausea (33%), fatigue (29%), headache (28%), and dyspnea (27%) and in the 90-180 mg group were nausea (40%), diarrhea (38%), fatigue (36%), cough (34%), and headache (27%).

**DRUG INTERACTIONS**

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**Please see Brief Summary of the Full Prescribing Information on the following pages.**

**References:**

briefer summary of prescribing information

6 adverse reactions

these topics do not include the information needed to use alunbrig safely and effectively. see full prescribing information for alunbrig.

6.1 clinical trial experience

the adverse reactions listed in the table are discussed in greater detail in other sections of the prescribing information.

table 3 summarizes the incidence of treatment-related adverse reactions and laboratory abnormalities observed in all patients across both regimens in trials 1 and 2. table 3 summarizes the incidence of treatment-related laboratory abnormalities observed in all patients across both regimens in trials 1 and 2.

7.2 drugs that may decrease brigatinib plasma concentrations

brigatinib is a CYP3A inducer and may decrease concentrations of CYP3A substrates. avoid the concomitant use of strong CYP3A inducers with alunbrig, including but not limited to rifampin, carbamazepine, phenytoin, and phenobarbital.

6.1 clinical trial experience

the safety of alunbrig was evaluated in 219 patients with locally advanced or metastatic ALK-positive NSCLC in two trials (ALTA and LUMA). 145 patients were treated with alunbrig 90 mg once daily and 74 patients were treated with alunbrig 180 mg once daily. of the 145 patients treated in trial ALTA, 82 were treated with alunbrig 90 mg once daily and 63 were treated with alunbrig 180 mg once daily. of the 74 patients treated in trial LUMA, 37 were treated with alunbrig 90 mg once daily and 37 were treated with alunbrig 180 mg once daily.

6.1 clinical trial experience

adverse reactions that occurred in ≥5% of patients treated with alunbrig 90 mg or 180 mg are summarized in tables 1 and 2.

5.1 hyperglycemia

monitor patients for any signs or symptoms of diabetes during treatment with alunbrig. advise patients to inform their healthcare provider about any unusual increase in thirst, urination, or hunger.

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In this guest commentary, Alice T. Shaw, MD, PhD, director of thoracic oncology at Massachusetts General Hospital Cancer Center, discusses the treatment of ALK-positive non-small cell lung cancer over the past decade.

I

n less than 6 years, five drugs have either been approved or granted priority review by the FDA for ALK-positive non-small cell lung cancer. ALK-positive NSCLC affects approximately 5% of patients with lung cancer. After discovery of the ALK gene as a target, which occurred about 10 years ago, we began testing the first-generation ALK inhibitor, crizotinib. Crizotinib (Xalkori; Pfizer, EMD Serono) showed robust antitumor activity in early clinical trials and was granted accelerated approval in 2011. It became the standard of care after two phase 3 trials demonstrated superiority compared with chemotherapy in the first-line and second-line settings. But, as we’ve seen with all targeted therapies, patients ultimately develop resistance, and resistance to crizotinib develops, on average, after about a year. As a result, there was an urgent need for other treatments.

Several groups have studied the molecular mechanisms of crizotinib resistance. This understanding fueled the development of multiple next-generation ALK inhibitors which are, in general, more potent than crizotinib and brain penetrant. Second-generation inhibitors approved by the FDA include ceritinib (Zykadia, Novartis), alectinib (Alecsensa; Genentech/Roche) and brigatinib (Alunbrig, Takeda). These agents, which are all approved for patients who fail crizotinib, have excellent antitumor activity in clinical trials.

The fifth drug that is likely to be approved is the third-generation ALK inhibitor lorlatinib (PF-06463922, Pfizer). Based on promising data from a phase 1/2 study, this agent has been granted priority review by the FDA. This is an important drug, because while second-generation inhibitors are highly effective, patients will develop resistance. Patients also frequently relapse in the central nervous system. In clinical trials, lorlatinib showed marked activity in patients previously treated with one or more ALK inhibitors, including in the CNS. Thus, lorlatinib may be effective for patients who have received first- and/or second-generation ALK inhibitors. While the timing of drug development has helped foster a sequential approach to treatment, the optimal sequence is under active investigation. In particular, more potent next-generation ALK inhibitors have been or are now being tested in the first-line setting. For example, in ASCEND-4, ceritinib was compared head-to-head against platinum/pemetrexed chemotherapy and shown to be superior in terms of PFS and response rate. Median PFS with first-line ceritinib was 16.6 months compared with 8.1 months with standard chemotherapy. As a result, ceritinib gained FDA approval for both crizotinib-naive and crizotinib-treated patients.

Of the all recent studies in the ALK field, perhaps the most practice-changing has been the global ALEX trial, which compared alectinib head-to-head with crizotinib as first-line therapy. This study demonstrated that alectinib was superior to crizotinib, with a median PFS of 25.7 months versus 10.4 months, per independent review. Alectinib was also notably more active in the CNS, significantly decreasing the cumulative incidence of CNS progression. In terms of safety, alectinib had a similar to slightly more favorable safety profile than crizotinib. These results have led to a rapid shift where alectinib, not crizotinib, is standard first-line therapy in many countries, including the United States.

We are awaiting the results of several phase 3 trials comparing next-generation ALK inhibitors to crizotinib, not alectinib. Thus, establishing the most active first-line therapy may be tricky, as it will involve cross-trial comparisons. The CROWN study comparing lorlatinib with crizotinib as first-line therapy is of particular interest given the broad activity of lorlatinib against all known single ALK resistance mutations, with the potential to completely suppress the development of on-target resistance.

While patients can derive significant benefit from sequential ALK inhibitors, at some point, they may no longer respond to single-agent ALK inhibitors. In some cases, resistant cancers have activated other signaling pathways which bypass inhibition of ALK. Preclinical studies have identified a variety of bypass signaling pathways capable of mediating resistance, including EGFIR, cKIT, MET and SRC, among others. These studies have identified potential combination strategies, the most promising of which include combination of ALK/MEK inhibitors and ALK/SHP2 inhibitors. These combinations could be effective in overcoming resistance that is due to bypass signaling. It is also possible that combinations could significantly delay or even prevent resistance, which could justify further development of these treatments.

Guest Commentary: Research explores first-line approvals, combination therapy

Brigatinib demonstrates safety, efficacy in crizotinib-resistant disease

Brigatinib demonstrated enduring efficacy and tolerable safety when administered at 90-mg and 180-mg doses, as well as increased PFS and greater interstitial activity at the higher dose, according to updated results from the phase 2 ALTA trial presented at World Conference on Lung Cancer.

The 180-mg dose was preceded by a 7-day lead-in dose at 90 mg, the researchers noted. “Brigatinib [Alunbrig, Takeda], a next-generation ALK inhibitor, recently received accelerated approval in the United States for the treatment of patients with metastatic ALK-positive NSCLC who have progressed on or are intolerant to crizotinib,” the researchers wrote. “We report updated data from the randomized phase 2 trial, which was designed to investigate the efficacy and safety of 2 brigatinib regimens in patients with crizotinib-refractory, advanced ALK-positive NSCLC.”

Myung Ju Ahn, MD, PhD, professor in the department of hematology and oncology at Samsung Medical Center in Seoul, and colleagues examined the efficacy and safety of the 90-mg and 180-mg dosing regimens across 222 patients with crizotinib-refractory, advanced ALK-positive NSCLC. They categorized patients according to the existence of brain metastases at baseline and best response to prior treatment with crizotinib.

Researchers randomly assigned patients 1:1 to treatment with brigatinib 90 mg once daily (arm A; n = 112) or 180 mg once daily after lead-in treatment for 7 days (arm B; n = 110). Investigator-assessed confirmed objective response rate per RECIST 1.1 served as the primary endpoint.

Patients in arm A were younger than patients in arm B (51 years vs. 57 years) and more patients in arm A had brain metastases (71% vs. 67%). More patients in arm A had measurable brain metastases at baseline (26 vs. 18). At data cutoff, median follow-up was 16.8 months in arm A and 18.6 months in arm B. At that point, more patients in arm B continued to receive brigatinib than in arm A (41% vs. 32%).

Confirmed ORR was 51% in arm A and 55% in arm B. Median PFS was higher in arm B than in arm A (16.7 months vs. 9.2 months).

Brigatinib continues on page 15

Disclosure: Lin reports a consultant/advisory role with Boehringer Ingelheim and honoraria from Chugai Pharmaceuticals.

PERSPECTIVE

Brigatinib (Alunbrig, Anc) was granted accelerated FDA approval in April 2017 for the treatment of patients who have progressed on, or are intolerant to, crizotinib. Brigatinib is a second-generation ALK inhibitor that offers several advantages over crizotinib.

One of the main issues with crizotinib is that it has limited activity in the brain, which therefore becomes a common site of disease progression. The second issue is that tumors inevitably develop resistance to crizotinib, which means most patients experience disease relapse within one to two years.

Next-generation ALK inhibitors like brigatinib are more potent against ALK; they also have enhanced ability to permeate the central nervous system. Additionally, brigatinib can target most resistance mutations in the ALK tyrosine kinase domain that emerge in patients who have been treated with crizotinib. The response rates with brigatinib among patients previously treated with crizotinib are quite high, making brigatinib a great option for patients who progress on crizotinib.

Important questions have emerged as we move forward with the next-generation ALK inhibitors. The first question arises from the global ALEX trial data, which demonstrated the superior efficacy of first-line alectinib compared with crizotinib. This data effectively establishes alectinib as the standard first-line therapy for ALK-positive NSCLC. It will therefore be important to understand how effective brigatinib is among those patients who progress on alectinib.

It is notable that, while brigatinib harbors activity against most crizotinib-resistant ALK mutations, its clinical activity against the G1202R mutation has yet to be established. This resistance mutation emerges most commonly after patients progress on a next-generation ALK inhibitor and has been particularly challenging to target. We have also seen the G1202R mutation emerge in patients who progress on brigatinib.

Another question is how effective brigatinib will be in the first-line setting, which is being investigated in the phase 3 ALTA-1L trial. However, it is worth noting that participants in this trial are being randomized to brigatinib versus crizotinib. Therefore, it will not address how first-line brigatinib may compare to first-line alectinib.

Research continues on page 11
Alectinib improved several disease measurements among patients with previously treated ALK-positive non-small cell lung cancer, including PFS and central nervous system overall response rate, according to findings presented at the European Society for Medical Oncology Congress. “[The] current standard of care [for ALK-positive NSCLC] is crizotinib,” the researchers wrote. “However, many patients experience progressive disease within a year, often in the central nervous system. The phase 3 ALUR study investigated efficacy and safety of alectinib vs. standard relapse chemotherapy in ALK-positive NSCLC previously treated with platinum-based doublet chemotherapy and crizotinib.”

Silvia Novello, MD, PhD, assistant professor in the thoracic oncology unit at San Luigi Hospital in Orbassano, Italy, and colleagues examined the safety and efficacy of alectinib vs. standard relapse chemotherapy among 107 patients aged 18 years and older. Patients were randomly assigned 2:1 to treatment with alectinib 600 mg twice per day or chemotherapy (pemetrexed 500 mg/m² every 3 weeks or docetaxel 75 mg/m² every 3 weeks) until disease progression, death, or withdrawal. Patients could switch from chemotherapy to alectinib following disease progression. PFS by investigator assessment served as the primary outcome; secondary outcomes included PFS by independent review committee, overall response rate and CNS ORR by independent review committee; disease control rate; duration of response and safety.

Most patients (n = 72) were treated with alectinib; the rest (n = 35) received chemotherapy. Almost all patients (n = 104) received one or more doses of study drug (alectinib, n = 70; chemotherapy, n = 34).

Median treatment duration was 20.1 weeks with alectinib and 6 weeks with chemotherapy. Median follow-up at data cutoff was 6.5 months in the alectinib arm and 5.8 months in the chemotherapy arm.

Adverse events of all grades occurred in 77.1% of the alectinib arm and 85.3% of the chemotherapy arm, with grade 3 to 5 adverse events in 27.1% of the alectinib arm and 41.2% of the chemotherapy arm. Discontinuation of study treatment or dose reduction occurred in 10% of patients in the alectinib arm and 20.6% in the chemotherapy arm. One fatal adverse event occurred in the chemotherapy arm.

“Alectinib significantly improved systemic and CNS efficacy … vs. chemotherapy for previously treated ALK-positive NSCLC, with a favorable safety profile vs. chemotherapy,” the researchers wrote. “We evaluated the frequency and spectrum of ALK resistance mutations according to fusion variant [among] patients with ALK-Positive NSCLC with acquired tyrosine kinase inhibitor resistance and clinical outcomes of these patients who received various generations of ALK inhibitors.”

Jessica J. Lin, MD, clinical fellow in medicine and member of the thoracic cancers team at Massachusetts General Hospital, and colleagues examined the clinical efficacy of alectinib in the post-crizotinib setting. The results establish alectinib as the standard care for patients with ALK-positive NSCLC who have been treated with chemotherapy and crizotinib in countries and regions of the world where alectinib has not been approved or funded by insurance for first-line treatment of this disease.

ALK variants affect development of mutations, response to next-generation inhibitors

Certain ALK variants may correspond with the evolution of ALK resistance mutations, including G1202R, and could represent a molecular link between variants and clinical outcomes, according to findings published in Journal of Clinical Oncology. As a result, ALK variants may be a factor to consider when selecting next-generation ALK inhibitors.

“Emerging data indicate that ALK fusion variants may have biologic and clinical implications in ALK-positive lung cancer,” the researchers wrote. “We evaluated the frequency and spectrum of ALK resistance mutations according to fusion variant [among] patients with ALK-positive NSCLC with acquired tyrosine kinase inhibitor resistance and clinical outcomes of these patients who received various generations of ALK inhibitors.”

The researchers also evaluated 77 tumor biopsy specimens from patients with variants 1 and 3 who experienced disease progression after treatment with an ALK TKI. ALK resistance mutations occurred more often in variant 3 than in variant 1 (57% vs. 30%; P = .01) and the G1202R mutation was more common in variant 3 than in variant 1 (32% vs. 0%; P = .001).

The database with 577 patients highlighted comparable correlations between variant 3 and ALK resistance mutations, as well as G1202R (P = .01 and .015, respectively). The presence of variant 3 correlated with a substantial increase in PFS among patients treated with lorlatinib (PF-06463922, Pfizer) compared with variant 1 (HR = 0.31; 95% CI, 0.12-0.79).

“To our knowledge, we present the largest analysis to date to examine the clinical effect of ALK variants in ALK-positive NSCLC and the first study to evaluate ALK resistance mutations according to EML4-ALK variant,” the researchers wrote. “The findings suggest that EML4-ALK[variant] 3 is associated with a significantly higher incidence of ALK resistance mutations, particularly G1202R, and provides a potential molecular link between variant and clinical outcome. Thus, ALK variant status may represent an important emerging factor in guiding the treatment strategy for ALK-positive NSCLC.”


Disclosures: Lin reports a consultant/advisory role with Boehringer Ingelheim and honoraria from Chugai Pharma. Please see the full study for a list of all other authors’ relevant financial disclosures.
lorlatinib appears to have both systemic and intracranial activity among previously treated patients with advanced ALK-positive or ROS1-positive non-small cell lung cancer, according to findings from a phase 1 dose-escalation study published in The Lancet Oncology.

“Lorlatinib (PF-06463922, Pfizer) is a novel, oral, reversible, ATP-competitive macrocyclic tyrosine kinase inhibitor that targets ALK and ROS1,” the researchers wrote. “Preadministrative studies suggest that lorlatinib might be an effective therapeutic strategy for ALK-positive and ROS1-positive patients who have relapsed after treatment with available [TKIs]. We aimed to assess the safety, maximum tolerated dose and antitumor activity of lorlatinib in patients with advanced ALK-positive or ROS1-positive NSCLC.”

Alice T. Shaw, MD, PhD, director of thoracic oncology at Massachusetts General Hospital Cancer Center, and colleagues enrolled 54 patients with advanced ALK-positive or ROS1-positive NSCLC in this international, multicenter, open-label, single-arm, first-in-man trial. The study required participants to be aged 18 years or older and have an ECOG performance status of 0 or 1, as well as adequate end-organ function.

Most patients (77%) had ALK-positive NSCLC. Twelve patients (23%) were ROS1-positive; one patient had unconfirmed ALK and ROS1 status. More than half of the study population (52%) had been treated with two or more TKIs and most patients (72%) had central nervous system metastases.

Patients received oral lorlatinib once or twice per day. Once-daily dosing ranged from 10 mg to 200 mg; twice-daily dosing ranged from 35 mg to 100 mg. At least three patients received each dose of lorlatinib. Some patients had tumor biopsies prior to treatment to categorize ALK resistance mutations.

Researchers analyzed safety among patients treated with at least one dose of lorlatinib. They analyzed efficacy in the intent-to-treat population, which included patients who had either ALK or ROS1 rearrangement and who received at least one dose of lorlatinib. Dose-limiting toxicities in cycle 1, according to investigator assessment, served as the primary endpoint; secondary endpoints included safety, pharmacokinetics and overall response.

The objective response rate was 46% among ALK-positive patients (n = 19; 95% CI, 31-63) and 42% among ALK-positive patients who had been treated with two or more TKIs (n = 11; 95% CI, 23-63). Among ROS1-positive patients, including 7 who had prior exposure to crizotinib, ORR was 50% (n = 6; 95% CI, 21-79).

The most frequent treatment-related adverse events included hypercholesterolemia (72%), hypertriglycerideremia (39%), peripheral neuropathy (39%) and peripheral edema (39%). One dose-limiting toxicity — grade 2 neurocognitive adverse events — occurred with the 200 mg dose. The patient experienced slow speech, mention and word-finding difficulty and did not complete at least 16 of 21 prescribed total doses in cycle one because of these toxicities, which were attributed to lorlatinib.

The researchers did not determine a maximum tolerated dose. The suggested dose for phase 2 was 100 mg once daily.

“One of our other questions was whether lorlatinib would be active in patients with brain metastases,” the researchers wrote. “The suggestion was that lorlatinib might be an effective agent for patients with brain metastases.”

Among ALK-positive patients who had progressed on previous ALK inhibitors, 13 patients received lorlatinib and continued to receive lorlatinib. In 11 patients treated with lorlatinib, ORR was 50% (n = 6; 95% CI, 21-79). In 10 patients, ORR was 50% (n = 5; 95% CI, 21-79).

Among ALK-positive and ROS1-positive patients with advanced ALK-positive NSCLC, the anterior visual fields were involved in 13 patients treated with lorlatinib. Of these patients, 10 (77%) had involvement of the left anterior visual field. Among 17 patients with involvement of the right anterior visual field, 16 (94%) had involvement of the right anterior visual field.

“Overall, lorlatinib is a novel, oral, reversible, ATP-competitive macrocyclic tyrosine kinase inhibitor that targets ALK and ROS1, as well as adequate end-organ function. However, the next-generation ALK inhibitors have demonstrated activity in the brain and have helped us to redefine how we measure benefit in clinical trials by shifting the focus to include a separate presentation of central nervous system efficacy and not just overall efficacy,” the researchers wrote.

This study from Shaw and colleagues looked at multiple doses of lorlatinib in both ALK- and ROS1-positive lung cancer. Lorlatinib, like some, but not all, ALK inhibitors is also a ROS1 inhibitor. A phase 2 study continued after the phase 1 portion, but the phase 1 report already included data to support lorlatinib submission to the FDA for use as a

Lorlatinib demonstrates safety, efficacy in previously treated NSCLC

In this guest commentary, David Ross Camidge, MD, PhD, Joyce Zeff Chair in lung cancer research at University of Colorado, explores the benefits and drawbacks of lorlatinib, a next-generation ALK/ROS1 inhibitor, for the treatment of ALK-positive non-small cell lung cancer.

The most frequent treatment-related adverse events included hypercholesterolemia (72%), hypertriglycerideremia (39%), peripheral neuropathy (39%) and peripheral edema (39%). One dose-limiting toxicity — grade 2 neurocognitive adverse events — occurred with the 200 mg dose. The patient experienced slow speech, mention and word-finding difficulty and did not complete at least 16 of 21 prescribed total doses in cycle one because of these toxicities, which were attributed to lorlatinib.

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to a patient sitting in front of us. Unfortunately, this study tended to lump things together, which means it takes a little work to unpack the data. For example, among the 12 patients with ROS1-positive NSCLC treated with lorlatinib, that 50% response rate reflects 6 responding patients, 4 of whom were ineligible for study because they had received prior crizotinib; the overall response rate after crizotinib—which is the real unmet clinical need—was only achieved in 2 of 7 patients.

The unmet clinical need in the ALK domain is no longer after the failure of crizotinib, but after failure of one of the approved next-generation inhibitors. Therefore, it is impressive that lorlatinib demonstrated a response in 11 of 26 patients (42%) who had received two or more prior ALK inhibitors.

However, when trying to apply the efficacy data shown in the real world, this approach (and the planned FDA label) presupposes that all such ALK inhibitors are equivalent. The immediate post-crizotinib setting—the most clearly defined clinical scenario in which to compare next-generation agents—these drugs are really not equivalent. Response rates for alectinib, brigatinib and ceritinib mostly range from 50% to 60% and all agents consistently demonstrate activity against a comparable frequency of common crizotinib-resistance mechanisms, but where they differ considerably is in drug-resistant disease control.

With astonishing reliability across studies, ceritinib has a median PFS post-crizotinib of approximately 6 to 7 months; PFS post-brigatinib is 8 to 9 months for alectinib and 15 to 16 months for brigatinib. For Brigatinib, this represents nearly a doubling of PFS information. In the phase 2 trial of lorlatinib, the CNS response seems to gradually increase relative to the overall response with rising doses in the CNS—there are no doses available for analysis. All patients with a recognizable ALK mutation, including 5 patients with G1202R-site mutations, responded. In contrast, none of the patients without an identifiable ALK mutation responded, which is consistent with the potential problem of as-yet undefined second drivers.

Intriguingly, those most predisposed to developing mutations may be influenced by the specific break point in the EML4 gene in the rearrangement. Data show that variant 3, which represented 40% of the EML4-ALK cases analyzed, appeared associated with a much higher rate of mutations, including G1202R, than variant 2, which represented 43% of EML4-ALK cases. The median PFS with lorlatinib in this retrospective analysis was much longer for variant 3 than for variant 1 (11 months vs. 3.3 months), which, again, is consistent with a mutational context that will likely be limited to the CNS, the site where lorlatinib may have limited clinical activity against G2032R.

The confirmed intracranial ORR among patients with measurable brain metastases at baseline was 50% in arm A and 67% in arm B. Median intracranial duration of response was 16.6 months in arm B and not reached in arm A.

The most frequent treatment-related adverse events included nausea (38% in arm A and 47% in arm B), diarrhea (28% and 44%), cough (28% and 40%), headache (30% and 35%) and vomiting (36% and 30%). The most frequent treatment-related adverse events of grade 3 or greater included increased creatinine phosphokinase (5% and 13%), hypertension (6% and 8%), pneumonia (4% and 5%), and increased lipase (5% and 4%). Arm B demonstrated higher incidences of dose reduction (30% vs. 9%) and discontinuation (11% vs. 4%) due to treatment-related adverse events.

“Brigatinib continues to show substantial efficacy and acceptable safety at both dose levels, with numerically lower PFS and higher intracranial ORR at the recommended dosing regimen of 180 mg once daily (with lead-in) vs. 90 mg once daily,” the researchers wrote. – by Julia Ernst, MS

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drug failure of one or more prior ALK inhibitors. The objective response rate among 41 patients with ALK-positive disease was 46%. Among 12 patients with ROS1-positive NSCLC, the response rate was 50%.

These results sound promising, but we need to determine how we apply this

“One of the most fascinating things about the lorlatinib data is how they will force us to pull apart what contributes to an overall response rate dataset.”

DAVID ROSS CAMIGE, MD, PHD

“we will have to wait and see whether second-line PFS rankings will translate into similar first-line rankings.”

One of the good problems we are currently facing is that, if disease control for stage 4 ALK-positive lung cancer becomes measured in years with these next-generation drugs in the first-line setting, it is going to take a long time to see the data from the experimental arms of these trials to mature and be easily comparable.

There is the potential for multiple drug sequences to be possible in the future, with the potential problem of as-yet undefined second drivers.

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Disclosure: Camidge reports advisory board and consultation roles with AstraZeneca, Eli Lilly, Genentech, GlaxoSmithKline, and Novartis. Please see disclosure for full list of all other researchers' relevant financial disclosures.