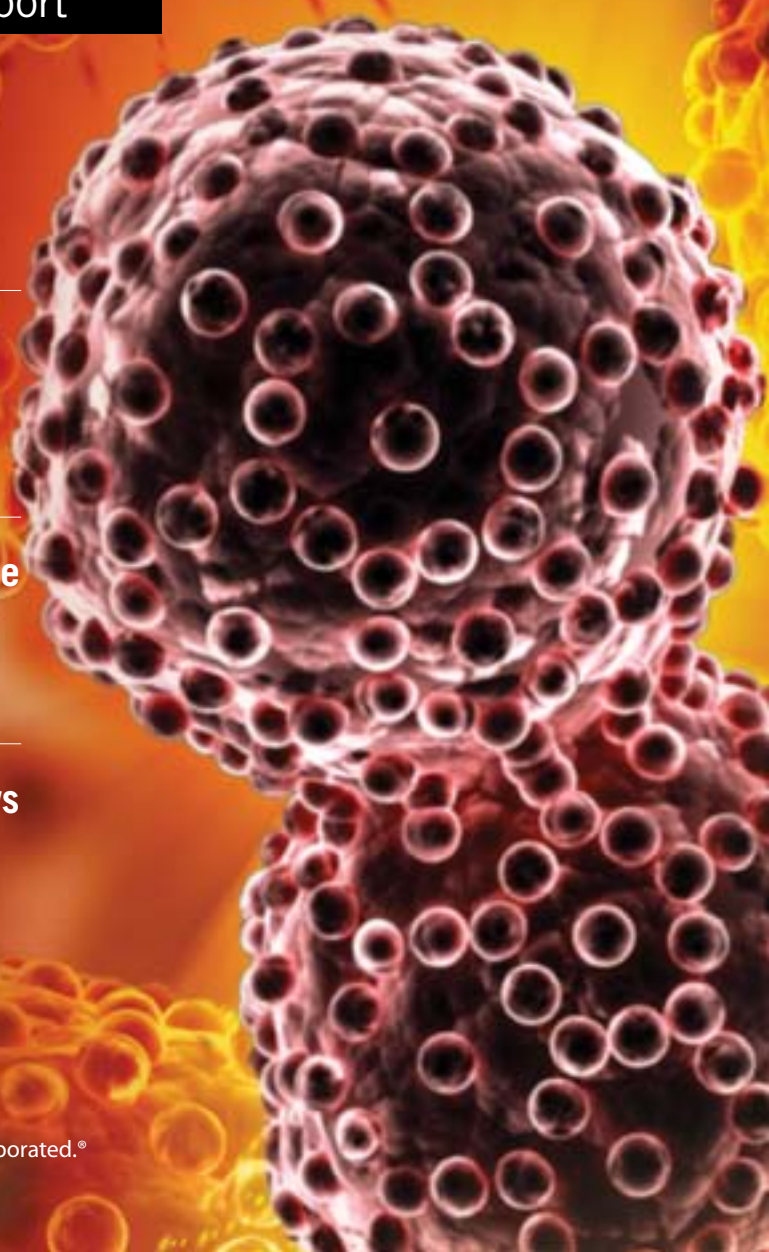
Supplement to
HemOnc today®

APRIL 25, 2018

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

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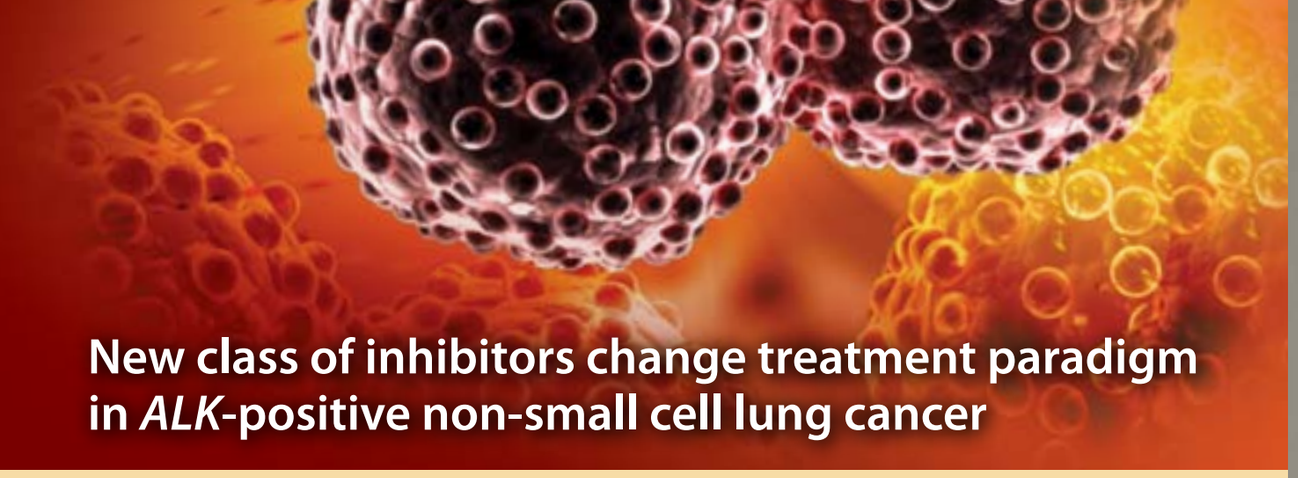

New class of inhibitors change treatment paradigm in *ALK*-positive non-small cell lung cancer

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 combatting 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

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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 nonsmokers. Physical inactivity also appeared associated with lung cancer mortality, which remained significant among nonsmokers.

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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

ALTA Efficacy Results	IRC Assessment[a]		Investigator Assessment[a]	
	90 mg once daily (n=112)	90→180 mg once daily[b] (n=110)	90 mg once daily (n=112)	90→180 mg once daily[b] (n=110)
Overall Response Rate, (95% CI)	48% (39-58)	53% (43-62)	45% (35-54)	54% (44-63)
Complete Response, n (%)	4 (3.6)	5 (4.5)	1 (0.9)	4 (3.6)
Partial Response, n (%)	50 (45)	53 (48)	49 (44)	55 (50)
Duration of Response, Median in Months (95% CI)	13.8 (7.4-NE)	13.8 (9.3-NE)	13.8 (5.6-13.8)	11.1 (9.2-13.8)

[b]180 mg once daily with a 7-day lead-in at 90 mg once daily.

Systemic follow-up data (18-month median follow-up) is consistent with 8-month median follow-up.[1]

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 180 mg of ALUNBRIG orally once daily with a 7-day lead in at 90 mg once daily (n=110, 18 with measurable brain metastases[c]), or 90 mg of ALUNBRIG orally once daily (n=112, 26 with measurable brain metastases[c]). The major efficacy outcome measure was confirmed objective response rate (ORR) 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 ORR, duration of response (DOR), intracranial ORR, and intracranial DOR.

Meaningful CNS Efficacy

Intracranial Objective Response in Patients With Measurable Brain Metastases[c] in ALTA	IRC Assessment[a]		Follow-Up Data (18-Month Median Follow-Up[d])[1,2]	
	90 mg once daily (n=26)	90→180 mg once daily[b] (n=18)	90 mg once daily (n=26)	90→180 mg once daily[b] (n=18)
Intracranial Overall Response Rate, (95 % CI)	42% (23-63)	67% (41-87)	50% (30-70)	67% (41-87)
Complete Response, n (%)	2 (7.7)	0	2 (8)	0
Partial Response, n (%)	9 (35)	12 (67)	11 (42)	12 (67)
Duration of Intracranial Response, Median (months) (range)	NE (1.9+ - 9.2+)	5.6 (1.9+ - 9.2+)	NR (3.7-NR)	16.6 (3.7-16.6)

[a]Median duration of follow-up was 8 months (range: 0.1-20.1).
[b]180 mg once daily with a 7-day lead-in at 90 mg once daily.
[c]≥10 mm in longest diameter (at baseline).
[d]Median duration of follow-up was 18-months (range:0.1-32).
CI, confidence interval; NE, not estimable; NR, not reached.

At the 8-month median follow-up, among the 23 patients who exhibited an intracranial response, 78% of patients in the 90-mg arm and 68% of patients in the 90→180-mg arm maintained a response for at least 4 months.

ALUNBRIG is the only ALK inhibitor with a one-tablet, once-daily recommended dosing regimen that can be taken with or without food.[e]

[e]The recommended dosing regimen is 90 mg orally once daily for the first 7 days. If tolerated during the first 7 days, increase dose to 180 mg orally once daily.

Visit **ALUNBRIG.com** to learn more.

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 hypertension occurred in 5.9% of patients overall. Control blood pressure prior to treatment with ALUNBRIG. 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 severity, resume ALUNBRIG at a reduced dose. Consider permanent discontinuation of treatment with ALUNBRIG for Grade 4 hypertension or recurrence of Grade 3 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. Grade 2 bradycardia occurred in 1 (0.9%) patient in the 90 mg group. Monitor heart rate and blood pressure during treatment with ALUNBRIG. Monitor patients 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. If a concomitant medication known to cause bradycardia is identified and discontinued 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 Disturbance: 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 macular edema and cataract occurred in one patient each in the 90→180 mg group. Advise patients to report any visual symptoms. Withhold ALUNBRIG and obtain an ophthalmologic evaluation 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.

Creatine Phosphokinase (CPK) Elevation: In ALTA, creatine phosphokinase (CPK) elevation occurred in 27% of patients receiving ALUNBRIG in the 90 mg group and 48% of patients in the 90→180 mg group. The incidence of Grade 3-4 CPK elevation was 2.8% in the 90 mg group and 12% in the 90→180 mg group. Dose reduction for CPK elevation occurred in 1.8% of patients in the 90 mg group and 4.5% in the 90→180 mg group. Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor CPK levels during ALUNBRIG treatment. Withhold ALUNBRIG for Grade 3 or 4 CPK elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

Pancreatic Enzyme Elevation: In ALTA, amylase elevation occurred in 27% of patients in the 90 mg group and 39% of patients in the 90→180 mg group. Lipase elevations occurred in 21% of patients in the 90 mg group and 45% of patients in the 90→180 mg group. Grade 3 or 4 amylase elevation occurred in 3.7% of patients in the 90 mg group and 2.7% of patients in the 90→180 mg group. Grade 3 or 4 lipase elevation occurred in 4.6% of patients in the 90 mg group and 5.5% of patients in the 90→180 mg group. Monitor lipase and amylase during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 or 4 pancreatic enzyme elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

Hyperglycemia: In ALTA, 43% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 3.7% of patients. Two of 20 (10%) patients with diabetes or glucose intolerance at baseline required initiation of insulin while receiving ALUNBRIG. Assess fasting serum glucose prior to initiation of ALUNBRIG and monitor periodically thereafter. Initiate or optimize anti-hyperglycemic medications as needed. If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and consider reducing the dose of ALUNBRIG or permanently discontinuing ALUNBRIG.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to pregnant women. There are no clinical data on the use of ALUNBRIG in pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of ALUNBRIG.

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 pneumonia (5.5% overall, 3.7% in the 90 mg group, and 7.3% in the 90→180 mg group) and ILD/pneumonitis (4.6% overall, 1.8% 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 pneumonia (2 patients), sudden death, dyspnea, respiratory failure, pulmonary embolism, bacterial meningitis and urosepsis (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

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.

CYP3A Inducers: Avoid concomitant use of ALUNBRIG with strong CYP3A inducers.

CYP3A Substrates: Coadministration of ALUNBRIG with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of CYP3A substrates.

USE IN SPECIFIC POPULATIONS

Pregnancy: ALUNBRIG can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus.

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 women 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 with ALUNBRIG and for at least 4 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 3 months after the final dose.

Infertility: ALUNBRIG may cause reduced fertility in males.

Pediatric Use: The safety and efficacy of ALUNBRIG in pediatric patients have not been established.

Geriatric Use: Clinical studies of ALUNBRIG did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Of the 222 patients in ALTA, 19.4% were 65-74 years and 4.1% were 75 years or older. No clinically relevant differences in safety or efficacy were observed between patients ≥65 and younger patients.

Hepatic or Renal Impairment: No dose adjustment is recommended for patients with mild hepatic impairment or mild or moderate renal impairment. The safety of ALUNBRIG in patients with moderate or severe hepatic impairment or severe renal impairment has not been studied.

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

References: 1. Ahn M-J, Camidge DR, Tiseo M, et al. Oral presentation presented at: IASLC 18th World Conference on Lung Cancer; October 15-17, 2017; Yokohama, Japan. Abstract 8027. **2.** Ou S-HI, Tiseo M, Camidge DR, et al. Poster presented at the: Annual Congress of the European Society of Medical Oncology; September 8-12, 2017; Madrid, Spain. Poster 1345P.

Takeda ONCOLOGY

ALUNBRIG®
BRIGATINIB
180mg | 90mg | 30mg
TABLETS

BRIEF SUMMARY OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALUNBRIG safely and effectively. See full prescribing information for ALUNBRIG.

ALUNBRIG™ (brigatinib) tablets, for oral use
Initial U.S. Approval: 2017

1 INDICATIONS AND USAGE

ALUNBRIG is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease (ILD)/Pneumonitis

Severe, life-threatening, and fatal pulmonary adverse reactions consistent with interstitial lung disease (ILD)/pneumonitis have occurred with ALUNBRIG.

In Trial ALTA (ALTA), ILD/pneumonitis occurred in 3.7% of patients in the 90 mg group (90 mg once daily) and 9.1% of patients in the 90→180 mg group (180 mg once daily with 7-day lead-in at 90 mg once daily).

Adverse reactions consistent with possible ILD/pneumonitis occurred early (within 9 days of initiation of ALUNBRIG; median onset was 2 days) in 6.4% of patients, with Grade 3 to 4 reactions occurring in 2.7%.

Monitor for new or worsening respiratory symptoms (e.g., dyspnea, cough, etc.), particularly during the first week of initiating ALUNBRIG. Withhold ALUNBRIG in any patient with new or worsening respiratory symptoms, and promptly evaluate for ILD/pneumonitis or other causes of respiratory symptoms (e.g., pulmonary embolism, tumor progression, and infectious pneumonia). For Grade 1 or 2 ILD/pneumonitis, either resume ALUNBRIG with dose reduction after recovery to baseline or permanently discontinue ALUNBRIG. Permanently discontinue ALUNBRIG for Grade 3 or 4 ILD/pneumonitis or recurrence of Grade 1 or 2 ILD/pneumonitis.

5.2 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 hypertension occurred in 5.9% of patients overall.

Control blood pressure prior to treatment with ALUNBRIG. 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 severity, resume ALUNBRIG at a reduced dose. Consider permanent discontinuation of treatment with ALUNBRIG for Grade 4 hypertension or recurrence of Grade 3 hypertension.

Use caution when administering ALUNBRIG in combination with antihypertensive agents that cause bradycardia.

5.3 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. Grade 2 bradycardia occurred in 1 (0.9%) patient in the 90 mg group.

Monitor heart rate and blood pressure during treatment with ALUNBRIG. Monitor patients 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. If a concomitant medication known to cause bradycardia is identified and discontinued 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.

5.4 Visual Disturbance

In ALTA, adverse reactions leading to visual disturbance including blurred vision, diplopia, and reduced visual acuity, were reported in 7.3% of patients receiving ALUNBRIG in the 90 mg group and 10% of patients in the 90→180 mg group. Grade 3 macular edema and cataract occurred in one patient each in the 90→180 mg group.

Advise patients to report any visual symptoms. Withhold ALUNBRIG and obtain an ophthalmologic evaluation 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.

5.5 Creatine Phosphokinase (CPK) Elevation

In ALTA, creatine phosphokinase (CPK) elevation occurred in 27% of patients receiving ALUNBRIG in the 90 mg group and 48% of patients in the 90 mg→180 mg group. The incidence of Grade 3-4 CPK elevation was 2.8% in the 90 mg group and 12% in the 90→180 mg group.

Dose reduction for CPK elevation occurred in 1.8% of patients in the 90 mg group and 4.5% in the 90→180 mg group.

Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor CPK levels during ALUNBRIG treatment. Withhold ALUNBRIG for Grade 3 or 4 CPK elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

5.6 Pancreatic Enzyme Elevation

In ALTA, amylase elevation occurred in 27% of patients in the 90 mg group and 39% of patients in the 90→180 mg group. Lipase elevations occurred in 21% of patients in the 90 mg group and 45% of patients in the 90→180 mg group. Grade 3 or 4 amylase elevation occurred in 3.7% of patients in the 90 mg group and 2.7% of patients in the 90→180 mg group. Grade 3 or 4 lipase elevation occurred in 4.6% of patients in the 90 mg group and 5.5% of patients in the 90→180 mg group.

Monitor lipase and amylase during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 or 4 pancreatic enzyme elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

5.7 Hyperglycemia

In ALTA, 43% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 3.7% of patients. Two of 20 (10%) patients with diabetes or glucose intolerance at baseline required initiation of insulin while receiving ALUNBRIG.

Assess fasting serum glucose prior to initiation of ALUNBRIG and monitor periodically thereafter. Initiate or optimize anti-hyperglycemic medications as needed. If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and consider reducing the dose of ALUNBRIG or permanently discontinuing ALUNBRIG.

5.8 Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to pregnant women. There are no clinical data on the use of ALUNBRIG in pregnant women. Administration of brigatinib to pregnant rats during the period of organogenesis resulted in dose-related skeletal anomalies at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily) as well as increased post implantation loss, malformations, and decreased fetal body weight at doses of 25 mg/kg/day (approximately 1.26 times the human exposure at 180 mg once daily) or higher.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of ALUNBRIG.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the prescribing information:

- Interstitial Lung Disease (ILD)/Pneumonitis
- Hypertension
- Bradycardia
- Visual Disturbance
- Creatine Phosphokinase (CPK) Elevation
- Pancreatic Enzyme Elevation
- Hyperglycemia

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of ALUNBRIG was evaluated in 219 patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who received at least one dose of ALUNBRIG in ALTA after experiencing disease progression on crizotinib. Patients received ALUNBRIG 90 mg once daily continuously (90 mg group) or 90 mg once daily for 7 days followed by 180 mg once daily (90→180 mg group). The median duration of treatment was 7.5 months in the 90 mg group and 7.8 months in the 90→180 mg group. A total of 150 (68%) patients were exposed to ALUNBRIG for greater than or equal to 6 months and 42 (19%) patients were exposed for greater than or equal to one year.

The study population characteristics were: median age 54 years (range: 18 to 82), age less than 65 years (77%), female (57%), White (67%), Asian (31%), Stage IV disease (98%), NSCLC adenocarcinoma histology (97%), never or former smoker (95%), ECOG Performance Status (PS) 0 or 1 (93%), and brain metastases at baseline (69%).

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 pneumonia (5.5% overall, 3.7% in the 90 mg group, and 7.3% in the 90→180 mg group) and ILD/pneumonitis (4.6% overall, 1.8% 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 pneumonia (2 patients), sudden death, dyspnea, respiratory failure, pulmonary embolism, bacterial meningitis and urosepsis (1 patient each).

In ALTA, 2.8% of patients in the 90 mg group and 8.2% of patients in the 90→180 mg group permanently discontinued ALUNBRIG for adverse reactions. The most frequent adverse reactions that led to discontinuation were ILD/pneumonitis (0.9% in the 90 mg group and 1.8% in the 90→180 mg group) and pneumonia (1.8% in the 90→180 mg group only).

In ALTA, 14% of patients required a dose reduction due to adverse reactions (7.3% in the 90 mg group and 20% in the 90→180 mg group). The most common adverse reaction that led to dose reduction was increased creatine phosphokinase for both regimens (1.8% in the 90 mg group and 4.5% in the 90→180 mg group).

Table 3 and Table 4 summarize the common adverse reactions and laboratory abnormalities observed in ALTA.

Table 3: Adverse Reactions in ≥ 10% (All Grades*) or ≥ 2% (Grades 3-4) of Patients by Dose Group in ALTA (N=219)

Adverse Reactions	90 mg once daily N=109		90→180 mg once daily N=110	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	33	0.9	40	0.9
Diarrhea	19	0	38	0
Vomiting	24	1.8	23	0
Constipation	19	0.9	15	0
Abdominal Pain†	17	0	10	0
General Disorders And Administration Site Conditions				
Fatigue‡	29	1.8	36	0
Pyrexia	14	0	6.4	0.9
Respiratory, Thoracic And Mediastinal Disorders				
Cough	18	0	34	0
Dyspnea§	27	2.8	21	1.8‡‡
ILD/Pneumonitis	3.7	1.8	9.1	2.7
Hypoxia	0.9	0	2.7	2.7
Nervous System Disorders				
Headache¶	28	0	27	0.9
Peripheral Neuropathy#	13	0.9	13	1.8
Skin And Subcutaneous Tissue Disorders				
Rashᵖ	15	1.8	24	3.6
Vascular Disorders				
Hypertension	11	5.5	21	6.4
Musculoskeletal And Connective Tissue Disorders				
Muscle Spasms	12	0	17	0
Back pain	10	1.8	15	1.8
Myalgia**	9.2	0	15	0.9
Arthralgia	14	0.9	14	0
Pain in extremity	11	0	3.6	0.9
Metabolism And Nutrition Disorders				
Decreased Appetite	22	0.9	15	0.9
Eye Disorders				
Visual Disturbance††	7.3	0	10	0.9
Infections				
Pneumonia	4.6	2.8‡‡	10	5.5‡‡
Psychiatric Disorders				
Insomnia	11	0	7.3	0

*Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
†Includes abdominal distension, abdominal pain, and epigastric discomfort
‡Includes asthenia and fatigue
§Includes dyspnea and exertional dyspnea
¶Includes headache and sinus headache
#Includes peripheral sensory neuropathy and paresthesia
ᵖIncludes acneiform dermatitis, exfoliative rash, rash, pruritic rash, and pustular rash
**Includes musculoskeletal pain and myalgia
††Includes diplopia, photophobia, blurred vision, reduced visual acuity, visual impairment, vitreous floaters, visual field defect, macular edema, and vitreous detachment
‡‡Includes one Grade 5 event

Table 4: Laboratory Abnormalities in ≥20% (All Grades*) of Patients by Regimen in ALTA (N=219)

Laboratory Abnormality	90 mg once daily N= 109		90→180 mg once daily N=110	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
Increased aspartate aminotransferase	38	0.9	65	0
Hyperglycemia†	38	3.7	49	3.6
Increased creatine phosphokinase	27	2.8	48	12
Increased lipase	21	4.6	45	5.5
Increased alanine aminotransferase	34	0	40	2.7
Increased amylase	27	3.7	39	2.7
Increased alkaline phosphatase	15	0.9	29	0.9
Decreased phosphorous	15	1.8	23	3.6
Prolonged activated partial thromboplastin time	22	1.8	20	0.9
Hematology				
Anemia	23	0.9	40	0.9
Lymphopenia	19	2.8	27	4.5

*Per CTCAE version 4.0
†Elevated blood insulin was also observed in both regimens

7 DRUG INTERACTIONS

7.1 Drugs That May Increase Brigatinib Plasma Concentrations

Strong CYP3A Inhibitors

Coadministration of itraconazole, a strong CYP3A inhibitor, increased brigatinib plasma concentrations and may result in increased adverse reactions. Avoid the concomitant use of strong CYP3A inhibitors with ALUNBRIG, including but not limited to certain antivirals (e.g., boceprevir, cobicistat, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir), macrolide antibiotics (e.g., clarithromycin), antifungals (e.g., itraconazole, ketoconazole, posaconazole, voriconazole), and conivaptan. Avoid grapefruit or grapefruit juice as it may also increase plasma concentrations of brigatinib. If concomitant use of a strong CYP3A inhibitor cannot be avoided, reduce the dose of ALUNBRIG by approximately 50%.

7.2 Drugs That May Decrease Brigatinib Plasma Concentrations

Strong CYP3A Inducers

Coadministration of ALUNBRIG with rifampin, a strong CYP3A inducer, decreased brigatinib plasma concentrations and may result in decreased efficacy. Avoid the concomitant use of strong CYP3A inducers with ALUNBRIG, including but not limited to rifampin, carbamazepine, phenytoin, and St. John's Wort.

7.3 Drugs That May Have Their Plasma Concentrations Altered by Brigatinib

CYP3A Substrates

Brigatinib induces CYP3A in vitro and may decrease concentrations of CYP3A substrates. Coadministration of ALUNBRIG with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of CYP3A substrates.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to a pregnant woman. There are no clinical data on the use of ALUNBRIG in pregnant women. Administration of brigatinib to pregnant rats during the period of organogenesis resulted in dose-related skeletal anomalies at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily) as well as increased post-implantation loss, malformations, and decreased fetal body weight at doses of 25 mg/kg/day (approximately 1.26 times the human exposure at 180 mg once daily) or greater. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in which pregnant rats were administered daily doses of brigatinib during organogenesis, dose-related skeletal (incomplete ossification, small incisors) and visceral anomalies were observed at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily). Malformations observed at 25 mg/kg/day (approximately 1.26 times the human AUC at 180 mg once daily) included anasarca (generalized subcutaneous edema), anophthalmia (absent eyes), forelimb hyperflexion, small, short and/or bent limbs, multiple fused ribs, bent scapulae, omphalocele (intestine protruding into umbilicus), and gastroschisis (intestines protruding through a defect in the abdominal wall) along with visceral findings of moderate bilateral dilatation of the lateral ventricles.

8.2 Lactation

Risk Summary

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 for adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment with ALUNBRIG and for 1 week following the final dose.

8.3 Females and Males of Reproductive Potential

Contraception

ALUNBRIG can cause fetal harm.

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months after the final dose. Counsel patients to use a non-hormonal method of contraception since ALUNBRIG can render some hormonal contraceptives ineffective.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 3 months after the final dose.

Infertility

Based on findings in male reproductive organs in animals, ALUNBRIG may cause reduced fertility in males.

8.4 Pediatric Use

The safety and efficacy of ALUNBRIG in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of ALUNBRIG did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Of the 222 patients in ALTA, 19.4% were 65-74 years and 4.1% were 75 years or older. No clinically relevant differences in safety or efficacy were observed between patients ≥65 years and younger patients.

8.6 Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin within upper limit of normal [ULN] and AST greater than ULN or total bilirubin greater than 1 and up to 1.5 times ULN and any AST). The pharmacokinetics and safety of ALUNBRIG in patients with moderate or severe hepatic impairment have not been studied.

8.7 Renal Impairment

No dose adjustment is recommended for patients with mild and moderate renal impairment [creatinine clearance (CL_{cr}) 30 to 89 mL/min estimated by Cockcroft-Gault)]. The pharmacokinetics and safety of ALUNBRIG in patients with severe renal impairment (CL_{cr} 15 to 29 mL/min estimated by Cockcroft-Gault) have not been studied.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform patients of the following:

Interstitial Lung Disease (ILD)/Pneumonitis

Inform patients of the symptoms and risks of serious pulmonary adverse reactions such as ILD/pneumonitis. Advise patients to immediately report any new or worsening respiratory symptoms.

Hypertension

Advise patients of risks of hypertension and to promptly report signs or symptoms of hypertension.

Bradycardia

Advise patients to report any symptoms of bradycardia and to inform their healthcare provider about the use of heart and blood pressure medications.

Visual Disturbance

Advise patients to inform their healthcare provider of any new or worsening vision symptoms.

Creatine Phosphokinase (CPK) Elevation

Inform patients of the signs and symptoms of creatinine phosphokinase (CPK) elevation and the need for monitoring during treatment. Advise patients to inform their healthcare provider of any new or worsening symptoms of unexplained muscle pain, tenderness, or weakness.

Pancreatic Enzyme Elevation

Inform patients of the signs and symptoms of pancreatitis and the need to monitor for amylase and lipase elevations during treatment.

Hyperglycemia

Inform patients of the risks of new or worsening hyperglycemia and the need to periodically monitor glucose levels. Advise patients with diabetes mellitus or glucose intolerance that anti-hyperglycemic medications may need to be adjusted during treatment with ALUNBRIG.

Females and Males of Reproductive Potential

Embryo-Fetal Toxicity

Advise females and males of reproductive potential that ALUNBRIG can cause fetal harm.

- Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy and to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months after the final dose.
- Advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 3 months after the final dose.

Lactation

Advise females not to breastfeed during treatment with ALUNBRIG and for at least 1 week following the final dose.

Infertility

Advise males of reproductive potential of the potential for reduced fertility from ALUNBRIG.

Drug Interactions

Advise patients to inform their health care provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid grapefruit or grapefruit juice while taking ALUNBRIG.

Dosing and Administration

Instruct patients to start with 90 mg of ALUNBRIG once daily for the first 7 days and if tolerated, increase the dose to 180 mg once daily. Advise patients to take ALUNBRIG with or without food.

Missed Dose

Advise patients that if a dose of ALUNBRIG is missed or if the patient vomits after taking a dose of ALUNBRIG, not to take an extra dose, but to take the next dose at the regular time.

Please see full Prescribing Information for ALUNBRIG at ALUNBRIG.com.

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

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.*

In 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 as 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.


Alice T. Shaw

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 (Alecensa; 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 all the 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 *EGFR*, *cKIT*, *MET* and *SRC*, among others. These studies have identified potential combination strategies, the most promising of which include combinations 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 cre-

Research *continues on page 11*

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 intercranial 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 note.

"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 among 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 v1.1 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*

PERSPECTIVE


Jessica J. Lin

Brigatinib (Alunbrig, Ariad) 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 penetrate 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.

Jessica J. Lin, MD
Massachusetts General Hospital

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

Alectinib demonstrates safety, tolerability in previously treated patients

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/m^2 every 3 weeks or docetaxel 75 mg/m^2 every 3 weeks) until 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.

Median PFS by investigator assessment was 9.6 months (95% CI, 6.9-12.2) in the alectinib arm and 1.4 months (95% CI, 1.3–1.6) in the chemotherapy arm (HR = 0.15; 95% CI, 0.08-0.29). Median PFS by independent review committee was 7.1 months in the alectinib arm compared with 1.6 months in the chemotherapy arm (HR = 0.32; 95% CI, 0.17-0.59). ORR by independent review committee was 36.1% in the alectinib arm and 11.4% in the chemotherapy arm. CNS ORR among patients with measurable disease was 54.2% in the alectinib arm and 0% in the chemotherapy arm. The disease control rate was 80.6% in the alectinib arm and 28.6% in the chemotherapy arm. Median duration of response was 9.3 months in the alectinib arm (95% CI, 6.9 months-not estimable) and 2.7 months in the chemotherapy arm (95% CI, not estimable).

Adverse events of all grades occurred in 77.1% of the alectinib arm and 85.3% of the chemotherapy arm, with grade 3 to grade 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. - *by Julia Ernst, MS* ■

References:
Novello S, et al. Abstract 1299O_PR. Presented at: European Society for Medical Oncology Congress; Sept. 8-12, 2017; Madrid.

Disclosure: Novello reports speakers bureau roles with AstraZeneca, Bristol-Myers Squibb, Eli Lilly, MSD and Roche. Please see the full study for all other authors' relevant financial disclosures.

PERSPECTIVE

Sai-Hong I. Ou

The ALEX trial established alectinib as the standard of care for previously untreated patients with advanced *ALK*-positive NSCLC. The ALUR trial confirms the clinical efficacy of alectinib in the post-crizotnib setting. These results establish alectinib as the standard of 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.

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Disclosure: Ou reports advisory board roles with Ariad, Novartis, Pfizer, Roche and Takeda, as well as speakers bureau roles with Roche and Takeda.

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."

Jessica J. Lin

Jessica J. Lin, MD, clinical fellow in medicine and member of the thoracic cancers team at Massachusetts General Hospital, and colleagues examined data from 129 patients at Massachusetts General Hospital and the University of California, Irvine, with *ALK*-positive NSCLC and known *ALK* variants. Next-generation sequencing during regular care categorized a distinct group of 577 patients with *ALK*-positive NSCLC and known *ALK* variants; the researchers examined the rate and distribution of *ALK* resistance mutations in that cohort.

EML4-ALK fusion was present in 95% of the cohort of 129 patients. The most commonly observed *EML4-ALK* variants included variant 1 (43%) and variant 3 (40%). Researchers observed no differences in clinicopathologic features between patients with variant 1 and those with variant 3.

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%; $P = .023$) 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." – *by Julia Ernst, MS* ■

Reference:
Lin JJ, et al. *J Clin Oncol*. 2018;doi:10.1200/JCO.2017.76.2294.

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.

Research

continued from page 8

ates an argument for testing not only in the resistant setting but also in the upfront setting.

The field of *ALK*-positive lung cancer has moved at a phenomenal pace in the past decade. ALK inhibitors have fundamentally altered the natural history of *ALK*-positive NSCLC, improving not only prognosis but also quality of life. However, much more work remains. In particular, combination strategies are urgently needed for patients who no longer respond to ALK inhibitors. Patients with *ALK*-positive NSCLC also rarely respond to immunotherapy. Understanding the molecular basis for this, and developing more effective strategies to harness the immune system, represents another critical area of investigation. These and other studies will likely drive the next decade of research. ■

Disclosures: Shaw reports consultant roles with, and honoraria from, Ariad, Blueprint Medicines, Daiichi-Sankyo, EMD Serono, Foundation Medicine, Genentech/Roche, Ignyta, LOXO Oncology, Natera, Novartis, Pfizer and Takeda.

Lorlatinib demonstrates safety, efficacy in previously treated NSCLC

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. "Preclinical 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

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%), hypertriglyceridemia (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 slowed speech, mentation 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.

"After failure of a second-generation *ALK* [TKI], lorlatinib is effective in almost half of patients, probably corresponding to tumors with on-target resistance mechanisms and continued *ALK* dependency," the researchers wrote. "Although patients can notably benefit from sequential *ALK* [TKIs], the optimal sequencing of *ALK*-targeted agents remains to be established. On the basis of its efficacy in the resistant setting, lorlatinib is in phase 3 testing to investigate whether upfront treatment … can further improve clinical outcomes for patients with advanced *ALK*-positive NSCLC compared with crizotinib treatment."

– by Julia Ernst, MS ■

Reference:
Shaw AT, et al. *Lancet Oncol*. 2018; doi: 10.1016/S1470-2045(17)30680-0.

Disclosures: Shaw reports advisory board and consultant roles with Ariad, Blueprint Medicines, Daiichi Sankyo, EMD Serono, Genentech/Roche, Ignyta, KSQ, Loxo, Novartis, Pfizer and Taiho; honoraria from Foundation Medicine, Genentech/Roche, Novartis and Pfizer; and research funding through her institution from Genentech/Roche, Novartis and Pfizer. Pfizer funded the study. Please see the full study for all other authors' relevant financial disclosures.

Guest Commentary: Unpacking lorlatinib's promise

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 lorlatinib phase 1 dataset in the paper by Shaw and colleagues shows how our clinical development strategies are evolving as we extend control of molecularly specific subtypes of cancer. This ongoing trial has started to provide clues about what new attributes lorlatinib — which has a very different structure than approved ALK inhibitors — may bring to the treatment of *ALK*-positive lung cancer.

The first potential benefit of lorlatinib (PF-06463922, Pfizer) relates to coverage of *ALK* mutations that confer resistance to other ALK inhibitors. We know that if we start with first-generation crizotinib (Xalkori; Pfizer, EMD Serono), some acquired resistance is mediated by selecting out specific resistance mutations in the *ALK* gene. There are a range of crizotinib-resistant mutations and most of the next-generation ALK inhibitors — alectinib (Alecensa; Genentech/Roche), ceritinib (Zykadia, Novartis) and brigatinib (Alunbrig, Takeda) — have activity against many of them. However, these agents are not active against all crizotinib-resistant mutations, and they don't all provide the same spectrum of coverage. In preclinical experiments, lorlatinib appeared more potent than the other agents against a wider range of these mutations, including, in particular, one challenging mutation, G1202R.


David Ross Camidge

However, there are several factors that determine whether, and to what degree, these in vitro rankings matter clinically. The first is the patient's exposure to the different agents. If a patient is treated with a low-potency agent for a specific mutation, but the agent still covers that mutation, the preclinical ranking may not matter clinically. The second issue is the frequency with which each of these mutations drive resistance. If drug X is the only drug that can treat one particular mutation, but that mutation occurs rarely in the real world, the absolute impact of that benefit may be restricted to a niche population.

As an example of the former issue, brigatinib — the most recently licensed next-generation ALK inhibitor — appears on the cusp of inhibiting G1202R. Patient reports include examples where G1202R-positive cases appear sensitive to this drug, but G1202R has also been reported as a mechanism of resistance in others, presumably because of exposure differences between individuals. Broadening the spectrum of coverage by increasing the dose and resulting exposure may, for example, be one of the reasons why the median PFS appears to be much better for brigatinib 180 mg vs. 90 mg (15.6 months vs. 9.2 months).

With regard to the latter issue, the Massachusetts General group has shown, among patients who have a second biopsy after progression on a next-generation ALK inhibitor, as opposed to progression on crizotinib, that the problematic mutation — G1202R — becomes a more dominant mechanism of resistance. However, their most recently published series that includes patients who have been treated predominantly with crizotinib, alectinib or ceritinib still limits that mutation to only approximately 20% to 30% of cases.

One impending concern is mechanisms of resistance that act through means other than *ALK*. If we get to the point where a second molecular pathway becomes a codriver of the cancer, you could have the best ALK inhibitor in the world and it wouldn't be enough by itself. However, each of these drugs also have some targets separate from *ALK*, and each agent acts on different targets. For example, only crizotinib is also a *MET* inhibitor; only alectinib is also a *RET* inhibitor; and only brigatinib also has some activity in *EGFR* mutant cell lines, although the mechanisms by which that happens are unclear. Consequently, we may find additional differentiators of clinical efficacy emerge beyond *ALK* mutation coverage.

The second potential attribute of lorlatinib is that it is very good at getting into the brain. *ALK*-positive lung cancer may have a predilection for spreading to the brain; progression in the brain is also a known liability of crizotinib. Many of the next-generation ALK inhibitors have 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.

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's submission to the FDA for use as a

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drug after 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 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 treatment-naive. As 7 of the 12 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.

"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 CAMIDGE, MD, PHD

The unmet clinical need in the *ALK* data set 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. In the immediate post-crizotinib setting — the most cleanly defined clinical scenario in which to compare next-generation agents — these drugs are really not equivalent. Response rates for alectinib, ceritinib and brigatinib 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 duration of disease control.

With astonishing reliability across studies, ceritinib has a median PFS post-crizotinib of approximately 6 to 7 months; PFS post-crizotinib is 8 to 9 months for alectinib and 15 to 16 months for brigatinib. For brigatinib, this represents nearly a doubling of PFS compared with other drugs in cross-trial comparisons. Presumably, duration of control is a reflection of the drug's ability to suppress resistance from less common forms of resistance — in *ALK* or other drivers — in the body or brain that might otherwise emerge in the future. Among the 26 patients in the lorlatinib trial who had received two or more *ALK* tyrosine kinase inhibitors, only 2 had received brigatinib, with no documentation regarding the dose of brigatinib or whether they responded to lorlatinib.

In a small Japanese study, ceritinib conferred a 25% response rate post-alectinib, which might make one think we can just cycle through different ALK inhibitors and that lorlatinib leads the field in formally generating data in the setting of failure on multiple inhibitors. However, for certinib given post-alectinib, the duration of response was 6.3 months. In contrast, after two or more TKIs, the median duration of responses with lorlatinib was 11.7 months.

Perhaps 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. For many, this has been viewed as equivalent to the systemic (ie, extra-CNS) response rate, but an overall dataset can contain both CNS and extra-CNS information. In the phase 2 trial of lorlatinib, the CNS response seems to gradually increase relative to the overall response rate, especially with increasing lines of therapy. If we work under the presumptive explanation that prior drugs have relatively undertreated the brain, the CNS appears hyperresponsive at initiation of a drug such as lorlatinib that is highly penetrant in the CNS relative to the rest of the body, because it is behaving as if it has been exposed to fewer lines of therapy.

Seventy-two percent of patients had CNS disease at entry into the lorlatinib study by Shaw and colleagues. Unless we see the extra-CNS response rate presented separately from a composite CNS and extra-CNS overall dataset, we cannot exclude the fact that the overall response rate may be increased by hyperresponsive CNS lesions. The extra-CNS response rate may, therefore, be less than the overall response rate, especially after multiple lines of therapy or where systemic efficacy might be expected to be limited. For example, despite the promise of earlier preclinical reports, lorlatinib may have limited clinical activity against G2032R, a resistance mutation reported in as many as 41% of patients with *ROS1*-positive NSCLC after crizotinib.

In the phase 2 *ROS1* data presented for lorlatinib at the World Conference on Lung Cancer, the overall response rate was 36% among a largely crizotinib-pretreated population, but the CNS response rate was 56%. In other words, this represents a 36% relative reduction in response rate from the CNS to the overall dataset, with the overall dataset likely to include measurements from CNS target lesions within it. The key significance here is that, without seeing extra-CNS information directly, you cannot accurately tell a patient without CNS disease what the chances of a response will be.

The first glimpses of how such data will be presented are included in a waterfall plot of systemic (ie, extra-CNS) target lesion changes among the 12 patients with *ALK*-positive disease who had received 2 or more prior ALK inhibitors and who had pretreatment biopsies available for analysis. All patients with a recognizable *ALK* mutation, including 5 patients with G1202-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 1, 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 mutation-focused efficacy argument.

The manufacturers of lorlatinib also have an eye on approval as a first-line ALK inhibitor. An ongoing first-line trial called CROWN compares lorlatinib with crizotinib, although a comparable study, the ALEX trial, has already established alectinib as dramatically superior to first-line crizotinib. Similar studies with brigatinib (ALTA-1L) and ensartinib (X-396, Xcovery), another experimental ALK inhibitor (eXalt3), in comparison with crizotinib are also set to be published soon.

If you try to rank these drugs clinically by comparing their ability to control disease post-crizotinib, lorlatinib seems promising. Among 14 patients in the phase 1 trial who had received one prior TKI, the ORR for lorlatinib was 57% and the median PFS was 13.5 months; I am assuming that the TKI was crizotinib for most patients. However, 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 likely to encounter 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 for data in the experimental arms of these trials to mature and be easily comparable. There is the potential for multiple first- and second-line next-generation options in the future. Unless a clearly superior sequence emerges, relative to irrevocable detriment from choosing a different sequence, and until we identify a specific mutation to direct a specific drug to, the drug anyone reaches for first may end up being determined by much more basic things, including convenience (ie, pill burden), familiarity, cost and tolerability. ■

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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 creatine 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 longer 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* ■

Reference:
Ahn M-J, et al. Abstract 05.05. Presented at: World Conference on Lung Cancer; Oct. 15-18; Yokohama, Japan.

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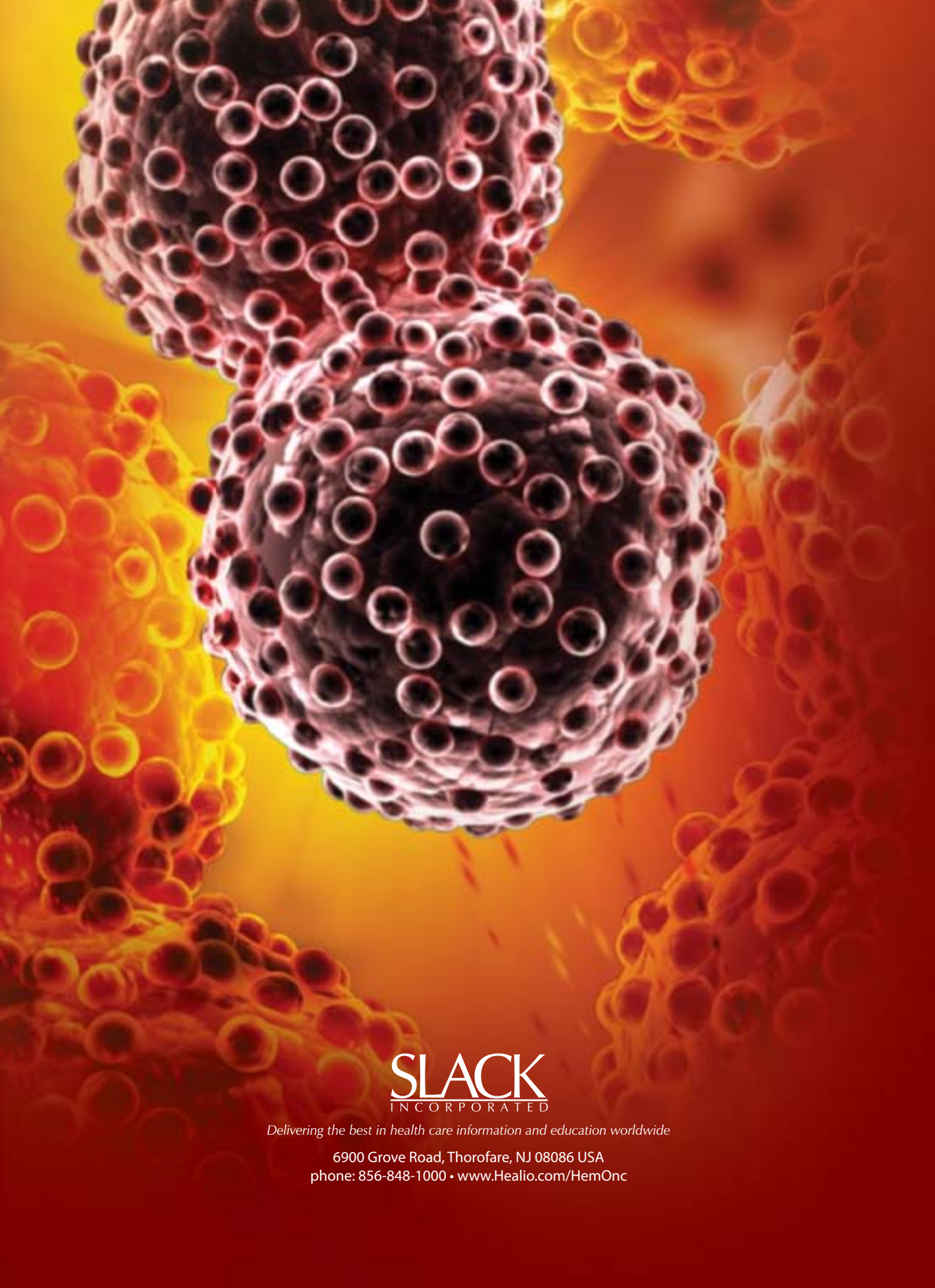

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