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Brigatinib: New-generation ALK inhibitor for nonsmall cell lung cancer

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ABSTRACT

Lung cancer, specifically nonsmall cell lung cancer (NSCLC) is the leading cause of death around the world. First-line therapies for metastatic NSCLC such as crizotinib, a tyrosine kinase inhibitor (TKI), have developed resistance due to a rearrangement of the anaplastic lymphoma kinase (ALK) gene. Brigatinib, approved in May 2016, is an ALK inhibitor specifically indicated for ALK-positive metastatic NSCLC in patients who have progressed on or resistant to crizotinib therapy. In several clinical trials, brigatinib has exhibited significant improvement in progression-free survival in patients that have experienced resistance to crizotinib therapy. The optimal dose of brigatinib was found to be 180 mg once daily and demonstrated greater efficacy as compared to its 90 mg once daily dose. Brigatinib was also found to be well tolerated. Although more studies are needed, the current data from these studies indicate brigatinib may be the most favorable therapeutic approach to treat NSCLC ALK-positive patients.

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Introduction

Targeted drug therapy in oncology has allowed researchers to develop specific drug products to recognize unique features of cancer cells. Recent advances in oncology have increased our understanding in the cellular signaling events that control tumor characteristics such as, insensitivity to growth inhibition, evasion of apoptosis, continuous replication, sustained angiogenesis, tissue invasion, and metastasis.[1]

One specific gene mutation is the anaplastic lymphoma kinase (ALK) gene which is involved in tumor progression and metastasis. The FDA recognizes the mutation of the ALK gene and approved targeted drug therapy. Drugs that target the ALK gene are known as tyrosine kinase inhibitors (TKIs). Patients with nonsmall cell lung cancer (NSCLC) have a rearrangement in the ALK gene. The ALK gene rearrangement produces an abnormal ALK protein cell signaling pathway and causes the cancer cells to grow and metastasize. TKIs interfere with the tyrosine kinase enzyme in this signaling pathway which results in growth inhibition of cancer cells. Cell signaling events in the absence of AKIs are mediated by tyrosine kinase enzymes that phosphorylate specific tyrosine residues to promote protein activation. This has led to the design and use of a new class of anticancer drugs known as TKIs which offer an innovative form of personalized therapy that target specific drivers of tumor growth. Therefore, TKIs play a critical role in the modulation of growth factor signaling. Activated forms of these enzymes can cause an increase in tumor cell proliferation and growth, and inhibits apoptosis effects. Upregulated tyrosine kinase signaling also promotes angiogenesis and metastasis.[1] Some of the drugs that target the abnormal ALK protein are crizotinib, ceritinib, alectinib, and brigatinib.[2] The first ever-approved ALK inhibitor by the US-FDA was crizotinib (Xalkori). This medication has also become the standard drug therapy for patients with metastatic ALK-positive NSCLC. However, the current problem with the standard therapy is the increasing number of cases of drug resistance. Most patients with ALK-positive lung cancer treated with crizotinib experience a relapse within a few years after initiating therapy.[3] The most common site of relapse in patients with ALK-positive NSCLC is the central nervous system.[4] Crizotinib is initially tolerated by majority of the patients. Crizotinib is also associated with minor or reversible vision changes. ALK inhibitors are well tolerated by many and offer therapeutic benefits in the beginning but drug resistance has been a challenge.[3] Another promising target for tumor specificity is epidermal growth factor receptor (EGFR). In cancer cells, EGFR is over expressed, dysregulated, or mutated. After extensive research, a relationship between EGFR signaling networks and cancer cell behavior was discovered. The Ras/mitogen-activated protein kinase and PI3K/Akt pathways are major signaling networks linking EGFR activation to cell proliferation and survival. EGFR signaling pathway genes have been found to be mutated in NSCLC. EGFR deregulation has been observed in multiple tumor types. EGFR is over expressed in NSCLCs of squamous cell subtypes.[5] EGFR inhibitors target these downstream signaling pathways. From this information, 2 drug classes were developed to inhibit downstream cell signaling pathways of EGFR. Cetuximab (Erbitux) targets the extracellular component of EGFR. Gefitinib (Iressa) and Erlotinib (Tarceva) are TKIs and they inhibit EGFR specifically to prevent downstream cell signaling and activation. Erlotinib is the first-line treatment and a maintenance therapy of EGFR-mutant NSCLC. It is also a second- or third-line treatment for patients with advanced stage NSCLC. Gefitinib is monotherapy treatment of locally advanced or metastatic lung cancer after failure on chemotherapy. The most common side effects of EGFR inhibitors are skin dryness, acne like rash on the scalp, diarrhea, and fatigue. EGFR inhibitors are similar to ALK inhibitors in regard to patients developing drug resistance.[6]

Through research and drug discovery, scientists were able to develop a new drug for patients that are resistant to the mainstay ALK-inhibitor, crizotinib. In May 2016, the FDA approved Brigatinib (Alunbrig) with “orphan drug status” for NSCLC. Brigatinib is an ALK inhibitor specifically used to treat patients with ALK-positive metastatic NSCLC and patients who have progressed on or resistant to crizotinib therapy. The FDA approval was mainly based on the results from Phase 2 ALTA (ALK in Lung Cancer Trial of AP26113) trial of brigatinib in adults.[7]

NSCLC is the leading cause of cancer-related deaths globally. In 2012, 1.8 million people worldwide were diagnosed with lung cancer resulting in 1.6 million deaths.[8] Most patients who have NSCLC are presented with advanced disease and generally result in poor prognosis and low survival rates. Active gene rearrangements in ALK account for approximately 3%-7% of NSCLC. Crizotinib can be associated with secondary resistance mutations in ALK gene.[9] Resistance mutations in ALK, including G1202R, have also been associated with the second-generation ALK inhibitors, ceritinib and alectinib. In the preclinical studies published by Ariad Publications in the journal of *Clinical Cancer Research*, brigatinib was shown to be highly potent and selectively inhibit ALK at lower concentrations than crizotinib, ceritinib, and alectinib. Seventeen ALK mutants that are associated with clinical resistance to other ALK inhibitors were tested. Brigatinib was the only inhibitor which showed activity against all 17 mutants tested including T11151Tins, L1152R, L1152P, C1156Y, F1174C, F1174L, F1174V, V1180L, L1196M, L1198F, D1203N, S1206F, S1206Y, E1210K, G1269A, I1171N V1180L, and G1202R.[10]

Clinical trials for brigatinib

The progression of NSCLC has been noted despite the use of current therapy. A remarkable clinical activity in patients suffering from ALK-rearranged NSCLC has been demonstrated by first-generation ALK inhibitor such as crizotinib. However, ALK-rearranged tumors have acquired resistance to crizotinib. Tumor insensitivity to crizotinib is known to arise from mutations to EGFR which can drive NSCLC to acquire resistance. ALK secondary mutations also play a role in the development of crizotinib resistance in 20%-40% of patients. The magnification of rearranged ALK gene is stated to be about 15% of crizotinib-refractory patients while activation of EGFR, KRAS, c-KIT, or IGF-IR cell signaling pathways are reported to be about 30% of patients.[11]

NCT02094573

A multicenter randomized phase II trial of AP26113 involving brigatinib in patients with ALK-positive NSCLC previously treated with crizotinib was conducted (ClinicalTrials.gov Identifier: NCT02094573). This study enrolled 222 subjects. The primary outcome was to measure the objective response rate of treatment. The authors evaluated the disappearance of all extranodal nontarget lesions, all lymph nodes must be nonpathologic in size (<10 mm), and normalization of tumor marker level. Inclusion and exclusion criteria for patients to participate in this study are located in Table 1. All participants must have a signed and dated informed consent to indicate that they were informed about possible risks and other necessary aspects of the study. The study results showed significant whole-body and intracranial response with good progression-free survival. This study found that 180 mg dose of brigatinib demonstrated greater efficacy compared to 90 mg dose of brigatinib.[12]

NCT02737501

ALTA-1L (ClinicalTrials.gov Identifier: NCT02737501) was a phase III multicenter open-label study involving brigatinib (AP 26113) against crizotinib in patients with ALK-positive advanced lung cancer. The study enrolled 275 subjects. Primary outcome was to evaluate progression-free survival as measured by a blinded independent review committee.[14] The trial is ongoing. Inclusion and exclusion criteria for patients to participate in this study are located in Table 2.

Table 1
Inclusion and exclusion criteria for patients to participate in multicenter randomized phase II trial of AP26113 involving brigatinib (ClinicalTrials.gov Identifier: NCT02094573)[13]

Inclusion criteria	Exclusion criteria
Age: 18 years old or older	Received any prior ALK-targeted TKI other than crizotinib
Gender: males and females	Received crizotinib within 3 days of the first dose of brigatinib (day 1, cycle 1)
Locally advanced or metastatic ALK-positive NSCLC	Received cytotoxic chemotherapy, investigational agents, or radiation within 14 days, except SRS or stereotactic body radiosurgery
Documented ALK rearrangement	Received monoclonal antibodies or had major surgery within 30 days of the first dose of brigatinib (day 1, cycle 1)
Negative pregnancy test	Have been diagnosed with another primary malignancy within the past 3 years (except for adequately treated nonmelanoma skin cancer, cervical cancer in situ, or prostate cancer, which are allowed within 3 years)
Must agree to use effective form of contraception while enrolled in the study	Have symptomatic CNS metastases that are neurologically unstable or require an increasing dose of corticosteroids
Progressive disease while receiving crizotinib	Have current spinal cord compression
Must not have received any other ALK inhibitors except crizotinib	Have significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to: myocardial infarction (MI), unstable angina, congestive heart failure (CHF), and cerebrovascular accident or transient ischemic attack within 6 months of first dose of brigatinib, history of clinically significant (as determined by the treating physician) atrial arrhythmia and any history of ventricular arrhythmia
At least one measurable lesion per response evaluation criteria in solid tumor version (RECIST v1.1)	History or the presence of pulmonary interstitial disease or drug-related pneumonitis
Recovered from any toxicities from prior use of anticancer therapies	An ongoing or active infection that requires intravenous (IV) antibiotics
Life expectance of greater than 3 months with satisfactory organ and hematological functions, and performance status $\leq$2 based on Eastern Cooperative Oncology Group	Have a history of or active significant gastrointestinal (GI) bleeding within 3 months of the first dose of brigatinib
Normal QT intervals of $\leq$450 ms in males and $\leq$470 ms in females	Known history of human immunodeficiency virus (HIV)
	Have malabsorption syndrome or other GI illness that could affect oral absorption of the study drug
	Pregnant or breastfeeding

RECIST, response evaluation criteria in solid tumors.

Table 2
Inclusion and exclusion criteria for patients to participate in phase III multicenter open-label study involving brigatinib (AP 26113) against crizotinib in patients with ALK-positive advanced lung cancer (ClinicalTrials.gov Identifier: NCT02737501)[14]

Inclusion criteria	Exclusion criteria
Age: 18 years old or older	Healthy volunteers
Gender: males and females	Received recent anticancer therapy for NSCLC
Documented rearranged ALK	Chemotherapy or radiation within 14 days prior to enrollment
Adequate tumor tissue available for central analysis	Received antineoplastic monoclonal antibodies within 30 days of the first dose of study drug
Histologically or cytological confirmed stage IIIB or stage IV NSCLC	Uncontrolled cardiovascular diseases
Recovered from previous anticancer therapy	Major surgery within 30 days of study enrollment
Adequate organ function	Ongoing infection
Eastern Cooperative Oncology Group status $\leq$2	Pregnancy or planning to get pregnant
Normal QT interval on screening ECG evaluation	

Table 3
Inclusion and exclusion criteria for patients to participate multicenter phase I/II study to determine safety, tolerability, pharmacokinetics, and preliminary antitumor activity of the oral ALK/EGFR inhibitor AP26113 (ClinicalTrials.gov Identifier: NCT01449461)[15]

Inclusion criteria	Exclusion criteria
Age: 18 years old or older	Healthy volunteers
Gender: males and females	Received investigational agent or systemic anticancer therapy 14 days prior to enrollment
Eastern Cooperative Oncology Group performance status of 0 or 1	Received any previous agents targeting ALK, except for crizotinib
Minimum of 3 months or more in life expectance	Significant cardiovascular diseases
Adequate hepatic, renal, and bone marrow function	History or presence of pulmonary diseases
Normal QT interval on ECG screening	Prolong QT or treated with agents known to induce Torsades de Pointes
Measurable disease by RECIST	Pregnant or breast feeding
Histologically confirmed advanced malignancies	

NCT01449461

Another multicenter phase I/II study was set to determine safety, tolerability, pharmacokinetics, and preliminary antitumor activity of the oral ALK/EGFR inhibitor AP26113 (ClinicalTrials.gov Identifier: NCT01449461). This study was conducted to evaluate the safety profile of oral administered brigatinib. The investigators evaluated the maximum oral-tolerated dose, dose limiting toxicities, pharmacokinetics profile, and recommended dose for phase II study.[15] The trial enrolled 137 patients who were grouped based on once daily dosage of 30 mg, 60 mg, 90 mg, 120 mg, 180 mg, and 240 mg. Inclusion and exclusion criteria for patients to participate in this study are located in Table 3.

Results from various brigatinib studies have demonstrated better efficacy outcomes compared to other ALK inhibitors such as crizotinib, ceritinib, and alectinib. The challenge with the treatment of ALK-positive NSCLC is the acquired resistance expressed by NSCLC. This type of resistance has led to insensitivity of standard available therapy particularly, crizotinib. Brigatinib has shown broad-spectrum activities against a variation of ALK and EGFR mutations which are believed to facilitate resistance. Contrary to crizotinib, the affinity for ALK is an important physicochemical feature expressed by brigatinib that contains a methoxy substituent, extended solubilization group and a chlorine atom. In addition, the incorporation of phosphorous-containing dimethyl phosphine oxide moiety which acts as a hydrogen acceptor increases the activity against ALK by 7-fold compared to analog with no substitution. It has been observed that an increase in tumor insensitivity for crizotinib is largely contributed by secondary mutations in ALK, whereas brigatinib in vitro activities have illustrated an ability to suppress emergence of any ALK secondary mutant when dosed at 180 mg in the phase I/II clinical trials (Table 4). [16]

Adverse effects

For patients with ALK-positive metastatic NSCLC, brigatinib is a viable treatmentAntineoplastic effect of brigatinib has been proven to be a great advantage for patients who have failed crizotinib treatment. Brigatinib, like most chemotherapeutic medications, can cause several adverse effects. Trials have experienced patient discontinuation due to some of the more severe adverse effects that have been observed.

Common side effects include nausea, diarrhea, fatigue, headaches, cough, and elevation of amylase. Brigatinib trials also observed death caused by several serious adverse effects that occurred within 30 days of treatment. Pulmonary embolism, pneumonia, pneumonitis, dyspnea, hypoxia, and respiratory failure were found to be the major causes of mortality mostly in patients with past medical history of these diseases. Other serious side effects that were not as-

Table 4
Significant ongoing clinical trials for brigatinib[12–17,19]

Study status	NCT #	Study title	Condition	Intervention	Adverse effects	Results
Active, not enrolling, results available	02094573	A study to evaluate the efficacy of brigatinib (AP26113) in participants with anaplastic lymphoma kinase (ALK)-positive, nonsmall cell lung cancer (NSCLC) previously treated with crizotinib	NSCLC	Brigatinib	Nausea 33%/40% diarrhea 19%/38% headache 28%/27% cough 18%/34% hypertension 6%/6% ↑lipase 4%/3% pneumonia 3%/5%	222 pts were enrolled (112 in arm A, 110 in arm B); median age was 54 years, 57% were female, 74% had received chemotherapy, and 69% had brain metastases. As of 29 February 2016, 57%/69% of pts in arms A/B were receiving BRG, with 7.8/8.3-month median follow-up. Per independent review committee, as of 16 May 2016, confirmed ORR was 48%/53% and median PFS was 9.2/15.6 months in arms A/B.
Active, not enrolling, interim results available	02737501	A phase 3 study of brigatinib vs crizotinib in ALK-positive advanced nonsmall cell lung cancer patients (ALTA-1L)	NSCLC	Brigatinib crizotinib	↑ Creatine kinase 39% cough 25% hypertension 23% ↑lipase 19%	A total of 275 patients underwent randomization; 137 were assigned to brigatinib and 138 to crizotinib. At the first interim analysis (99 events), the median follow-up was 11.0 months in the brigatinib group and 9.3 months in the crizotinib group. The rate of progression-free survival was higher with brigatinib than with crizotinib (estimated 12-month progression-free survival, 67% [95% confidence interval {CI}, 56-75] vs 43% [95% CI, 32-53]; hazard ratio for disease progression or death, 0.49 [95% CI, 0.33-0.74]; P <.001 by the log-rank test). The confirmed objective response rate was 71% (95% CI, 62-78) with brigatinib and 60% (95% CI, 51-68) with crizotinib; the confirmed rate of intracranial response among patients with measurable lesions was 78% (95% CI, 52-94) and 29% (95% CI, 11-52), respectively. No new safety concerns were noted.
Active, not enrolling, results available	01449461	A study to evaluate the safety, tolerability, pharmacokinetics and preliminary antitumor activity of the oral anaplastic lymphoma kinase (ALK)/epidermal growth factor receptor (EGFR) inhibitor brigatinib (AP26113)	NSCLC, lymphoma, large cell, anaplastic carcinoma	Brigatinib	Nausea 53% fatigue 43% diarrhea 41% headache and cough 39% ↑lipase 9% dyspnea 6% hypoxia 5% pneumonia 7%	Of 72 evaluable ALK + NSCLC pts, 52 (72%) responded: 45/65 (69%) with prior crizotinib and 7/7 crizotinib-naive pts. Median duration of response: 49 wk. Median progression-free survival (PFS): 56 wk; 47 wk with prior crizotinib. In a post hoc independent radiological review of pts with baseline intracranial central nervous system metastases, 6/12 pts with lesions ≥10 mm had a brain response (≥30% decrease in sum of longest diameters of target lesions) and 8/26 pts with only nonmeasurable lesions had disappearance of all lesions. Median intracranial PFS for these pts: 97 wk.

sociated with death in patients include bradycardia, hyperglycemia, hypertension, visual disturbances, and pancreatic toxicities. This leads to the conclusion that patients must be monitored for new or worsening respiratory toxicities and any other serious adverse effects.

Weaknesses

An in vitro study was conducted to test the resistance and cross resistance of 6 mutated forms of ALK including C1156Y, L1196M, L1152R, G1202R, G1269A, and S1206Y to crizotinib, AP26113, ASP3026, alectinib, and ceritinib using an NPM-ALK positive pro-B-cell line Ba/F3 model by proliferation assay and western blot. ALK phosphorylation status was analyzed after treatment with increasing drug doses. The study concluded that all strands were treatable by other medications except G1202R which was resistant to all. The L1152R-mutated gene was present in 1 μmol/L of crizotinib not correlating with the associated cell growth data. Therefore, this indicates moderate resistance leading to the possibility of minor error in the results which demonstrate a resistance to the medication. Because this is an in vitro study, the drugs used may not produce the same results in a human patient population. Although the results are promising, an in vivo trial may generate more reliable results.[20] Another preclinical trial evaluated the selectivity profile of brigatinib using engineered and cancer-derived cell lines both in vitro and in vivo in animals. Brigatinib was found to be the TKI of choice to maintain activity against certain mutated strands, G1202 R, of inhibitor resistant cell. All subjects used in vivo trial were animal subjects. Even though, the molecular findings were promising there is need for further investigation using human subjects to better understand the drug's selectivity and potency in the human body.[10] Consequently, further in-depth clinical trials for brigatinib should be conducted on patients with specific mutations in the ALK gene.

Several clinical and preclinical trials were undertaken to deliver studies that obtained clinically informative findings. There were, however, several limitations to these trials. The main limitation to all current trials is that majority of them are ongoing trials making their results incomplete. In addition, one particular trial by Cambridge et al that is evaluating safety and efficacy of brigatinib in advance malignancies is an open-label study. Another study by the same author is also an open-label, phase 3 trial which is comparing brigatinib versus crizotinib in ALK-positive NSCLC. Even though, these studies are ongoing once completed they will yet carry key limitations to their results; open-lable trials tend to introduce bias through unblinding.[18,19]

Another clinical trial used brigatinib in patients with NSCLC who have progressed after treatment with crizotinib. Patients received 90 mg, 180 mg, or 180 mg with a 7-day lead-in at 90 mg with 1 patient receiving 90 mg twice daily.[17] This variation in dosing regimens could create an error as each patient may react differently to various strengths of the medication. In addition, 16 patients died during or within 31 days of treatment which indicates a loss in the sample size making it difficult to conclude on the effects of the medication.[21] Kim et al evaluated the use of brigatinib in crizotinib-refractory ALK response to crizotinib in NSCLC. A total of 222 patients were entered and treated with either 90 mg once daily or 180 mg once daily with a 7-day lead-in at 90 mg once daily. The sample size was small, and patients were not evenly distributed as there were 164 patients who had received prior chemotherapy. This could have played a part in the treatment results as some patients may have experienced a level of therapeutic results after having been treated with other medications. Few patients had brain metastasis at baseline in each arm of treatment, this could mean that the disease has advanced in some more than others and therefore the results would be altered due to this factor. These limitations make it difficult to distinguish whether there was any influence on the results after the patients were treated with brigatinib.

Conclusions

There are several treatment options available for patients with ALK-positive NSCLC. These include crizotinib, ceritinib, alectinib, and lorlatinib. Although all these agents are unique and

have different degrees of efficacy, the development of resistance is a limiting factor to their effectiveness. On the other hand, brigatinib has demonstrated promising effectiveness against ALK-positive NSCLC in ongoing clinical trials. This is particularly significant for patients who have been taking crizotinib and have developed resistance due ALK rearrangement. The recommended dose for brigatinib is 90 mg once daily for 7 days; if tolerated, increase dose to 180 mg once daily. Patients experienced treatment effectiveness with limited side effects at these doses. Overall, brigatinib drug therapy can be a critical alternative in the treatment of ALK-positive NSCLC. Ongoing clinical trials will reveal more information regarding the toxicity profiles, pharmacokinetics, and efficacy of brigatinib.

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