Anaplastic lymphoma kinase (ALK) is a tyrosine kinase constitutively activated following chromosomal fusion/translocation in 3 to 7% of NSCLC patients. The primary endpoint was dose-limiting toxicity, and the secondary endpoints were efficacy, safety and pharmacokinetic (PK) analyses. Patients with ALK-positive NSCLC with progression of disease after crizotinib treatment, with ECOG performance status 0–2, and adequate organ function were eligible. Patients with symptomatic central nervous system (CNS) disease required treatment before participation in the study and stable CNS disease subsequently. Alectinib was administered orally at doses of 300, 460, 600, 760 and 900 mg BID until lack of clinical benefit, with intensive PK sampling performed. Efficacy was assessed by RECIST criteria v1.1. Toxicities were evaluated by CTCAE v4.0.

**FININDINGS**

No dose-limiting toxicities were observed up to the highest dose tested (900 mg BID) and only 1 patient required dose modification due to grade 2 fatigue. The most common adverse events (AEs) were fatigue, myalgia, cough, rash, peripheral edema, and creatinine phosphokinase and alanine aminotransferase increase. Grade 3/4 AEs included gamma-glutamyltransferase increase, neutropenia, hyperphosphatemia, hyperglycemia, syncope, renal failure and pericardial effusion. An objective overall response was observed in 54.5% across all the studied cohorts. Median PFS has not yet been reached, with 27 patients (73%) remaining on the study as of June 2013 with median treatment duration of 85 days (range 39–347 days). Alectinib is also active against CNS disease, as was shown in a separate abstract presented.
ALK inhibitor. During the 15th World Congress on Lung Cancer, results of a phase I dose-escalation trial of CH5424802 in patients with ALK-positive NSCLC who failed crizotinib therapy were presented, showing an overall response rate (ORR) of 54.5% for all cohorts and 59.5% in the 600 mg twice-daily dose cohort. Treatment was well tolerated with mainly grade 1/2 toxicities.

In a separate abstract, data were presented showing activity of CH5424802 in CNS metastatic disease. This is very encouraging. Second-generation ALK inhibitors like CH5424802 may provide clinically meaningful therapy for CNS disease, delaying implementation of radiation therapy, and improving quality of life and, hopefully, survival of these patients.

OTHER NEXT-GENERATION TKIS

Encouraging results from other trials of novel TKIs targeting ALK (including L1196M gatekeeper mutation), ROS1 and mutated EGFR in preclinical models were presented at the WCLC.

Results of the first-in-human dose-finding study of AP26113 [26] showed that among 24 evaluable ALK-positive patients, 15 responded to AP26113 and responses were observed in both crizotinib-naive (2/4; 50%) and crizotinib pretreated (13/17; 76%) patients. Among ALK-positive NSCLC patients with primary crizotinib-only treatment, 12/16 (75%) responded. Four out of 5 ALK-positive patients with untreated or progressing CNS lesions at baseline had evidence of radiographic improvement, including 1 patient resistant to crizotinib and LDK378.

LDK378 is another second-generation ALK inhibitor under clinical investigation in ALK-positive NSCLC. In a phase 1 study of 88 NSCLC patients who received LDK378 at 400–750 mg daily, the ORR was 70%, and in 64 crizotinib-resistant patients, it was 73%. Updated results of the phase 1 dose-escalation study with LDK378 in ALK-positive NSCLC were also presented. Among 18 patients (all doses), the overall response rate was 50%. Partial response was observed in 7/9 crizotinib-resistant patients. In patients pretreated with other ALK inhibitors, 3/5 had a partial response (including 2 patients who received CH5424802). An ongoing phase II study in ALK-positive NSCLC is evaluating LDK378 at a 750 mg dose (www.clinicaltrials.gov; NCT01685138).

CONCLUSION

ALK rearrangements, although present on average in 5% of NSCLC cases, translate into approximately 60,000 new patients with ALK-positive disease annually. With the approval of crizotinib, ALK-positive NSCLC is now recognized as a separate molecular and clinical subtype of NSCLC. Treatment with crizotinib showed improved clinical benefit when compared with the 60% ORR in this selected patient population. Unfortunately, as with all other targeted treatments, secondary resistance develops, usually within the first 12 to 24 months of treatment. New ALK inhibitors like LDK378, AP26113 or CH5424802 show not only better response rates in ALK-positive NSCLC when compared with crizotinib, but notably, activity against crizotinib-resistant disease, including CNS metastases.

Many questions remain, including the optimal sequence of treatment for ALK-positive disease and an effective strategy for treatment of resistant disease. However, emergence of these new, generally well-tolerated second-generation ALK inhibitors in clinical practice is anxiously awaited by patients and lung cancer oncologists.
References:


