Brigatinib

Brigatinib (previously known as **AP26113**) is an investigational small-molecule targeted cancer therapy being developed by ARIAD Pharmaceuticals, Inc.[1] Brigatinib has exhibited activity as a potent dual inhibitor of anaplastic lymphoma kinase (ALK) and epidermal growth factor receptor (EGFR).

ARIAD has begun a Phase 1/2 clinical trial of brigatinib based on cancer patients' molecular diagnoses in September 2011.

ALK was first identified as a chromosomal rearrangement in anaplastic large cell lymphoma (ALCL). Genetic studies indicate that abnormal expression of ALK is a key driver of certain types of non-small cell lung cancer (NSCLC) and neuroblastomas, as well as ALCL. Since ALK is generally not expressed in normal adult tissues, it represents a highly promising molecular target for cancer therapy.

Epidermal growth factor receptor (EGFR) is another validated target in NSCLC. Additionally, the T790M "gatekeeper" mutation is linked in approximately 50 percent of patients who grow resistant to first-generation EGFR inhibitors.[2] While second-generation EGFR inhibitors are in development, clinical efficacy has been limited due to toxicity thought to be associated with inhibiting the native (endogenous or unmutated) EGFR. A therapy designed to target EGFR, the T790M mutation but avoiding inhibition of native EGFR is another promising molecular target for cancer therapy.

1 Pre-clinical results

In 2010, ARIAD announced results of preclinical studies on brigatinib showing potent inhibition of the target protein and of mutant forms that are resistant to the first-generation ALK inhibitor, which currently is in clinical trials in patients with cancer. ARIAD scientists presented these data at the annual meeting of the American Association for Cancer Research (AACR) in Washington, D.C. in April.[3]

In 2011, ARIAD announced preclinical studies showing that brigatinib potently inhibited activated EGFR or its T790M mutant, both in cell culture and in mouse tumor models following once daily oral dosing. Importantly, the effective oral doses in these preclinical models were similar to those previously shown to be effective in resistant ALK models. When tested against the native form of EGFR, brigatinib lacked activity, indicating a favorable selectivity for activated EGFR. These data were presented at the International Association for the Study of Lung Cancer (IASLC) 14th World Conference on Lung Cancer.[4]

2 References

[1] Huang, Wei-Sheng; Liu, Shuangying; Zou, Dong; Thomas, Mathew; Wang, Yihan; Zhou, Tianjun; Romero, Jan; Kohlmann, Anna; Li, Feng. "Discovery of Brigatinib (AP26113), a Phosphine Oxide-Containing, Potent, Orally Active Inhibitor of Anaplastic Lymphoma Kinase". *Journal of Medicinal Chemistry*. doi:10.1021/acs.jmedchem.6b00306.

[2] Sequist; et al. (2011). "Genotypic and Histological Evolution of Lung Cancers Acquiring Resistance to EGFR Inhibitors". *Sci Trans. Med.* **3** (75): 75ra26. doi:10.1126/scitranslmed.3002003.

[3] "ARIAD Presents Preclinical Data on Its Investigational ALK Inhibitor, AP26113, Demonstrating That It Can Overcome Mutation-Based Drug Resistance in Cancer Models".

[4] "ARIAD Announces Presentation on Its Investigational Lung Cancer Drug Candidate, AP26113, a Dual Inhibitor of ALK and EGFR, at World Conference on Lung Cancer".

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3.1 Text

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