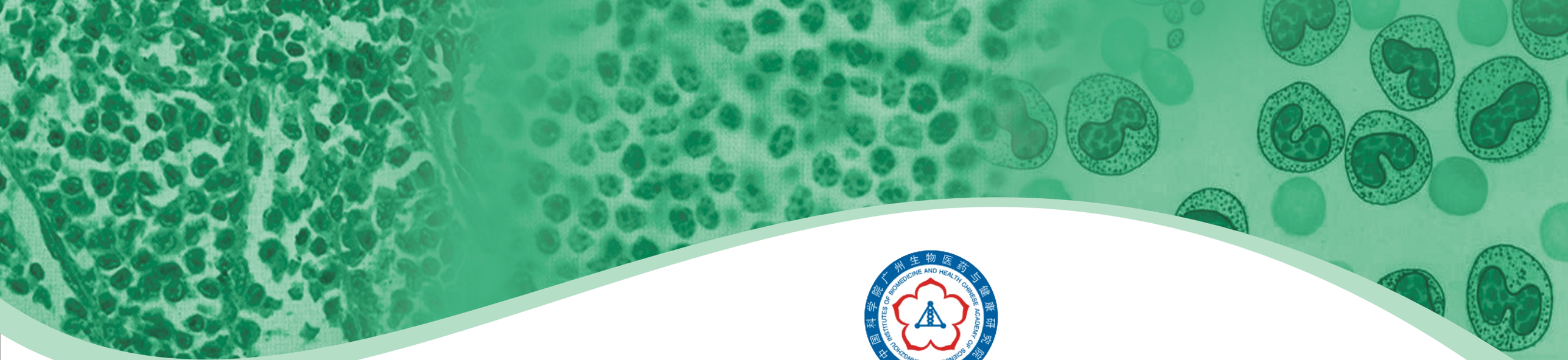

Contact Information

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Fact Sheet

D824

A Therapy for Chronic Myelogenous Leukemia

Innovation in the DDP

GIBH's Drug Candidate D824 Treatment for Drug-Resistant Leukemia

Product Description

D824 is a second generation Bcr-Abl kinase inhibitor for the oral treatment of resistant forms of chronic myelogenous leukemia (CML). D824 is a new class of Bcr-Abl kinase inhibitor that is active against the wild-type as well as several mutant forms of Bcr-Abl kinase that are primary responsible for CML resistance.

Indication and Market

CML has a high mortality rate of 20 to 30% just two years after a confirmed diagnosis. Approximately, 25% of patients with CML die every year and the average survival time is only 3 to 5 years. The age of onset ranges from 20 to 50 years of age and in China there are ~30,000 new cases diagnosed every year. The current frontline therapy, Gleevec is very effective and can alleviate the condition in many patients suffering from the disease. However, because of extensive usage of Gleevec, it is becoming less effective. Some CML patients are inherently resistant to Gleevec and some respond to Gleevec in the beginning, but acquire secondary resistance over the course of the treatment. Thus, there is a medical need to design new drugs that deal with CML resistance. The estimated market value of new drugs that aim to treat resistant forms of CML is estimated to be $250 to 500M per year after 3 years in the market.

Product Rationale

The major cause of resistance to Gleevec is a mutation (T315I) in the kinase domain of Bcr-Abl, representing about 20 to 30% of all known cases. Other common point mutations related to Gleevec resistance include E255K, E255V, T315I and D276G and D816 of c-KIT. Clinical drug resistance mediated by the T315I mutation of Bcr-Abl remains a significant medical problem and at this time there are no approved drugs targeting this mutant form of the enzyme. At GIBH we developed a new drug that effectively inhibits both the wild type and the T315I mutant form of Bcr-Abl kinase.

Preclinical Development

Preclinical studies have shown: (1) D824 inhibits Bcr-Abl kinase and the T315I mutant form effectively in cell based assays with IC_{50} values of 1.0 nM and 12 nM, respectively; (2) D824 inhibited other mutant forms of Bcr-Abl kinase with IC_{50} values less than 20 nM; (3) The drug has excellent anti-tumor activity in several in vivo xenograft animal models (including K562, Ku812, Bcr-Abl ^{WT}, Bcr-Abl ^{T315I}, Bcr-Abl ^{E255K}, Bcr-Abl ^{G250E} and Bcr-Abl ^{F317L}) at oral doses ranging from 2 to 5 mg/kg/day; (4) D824 has desirable PK properties, oral bioavailability (58.7%), a long half-life ($T_{1/2}$ = 8.7 hours) and a steady-state plasma concentration; (5) The compound demonstrated efficacy in a rodent model of leukemia with an IC_{50} value of less than 10 mg/kg/day; (5) Finally, D824 has a reasonable safety profile (LD_{50} > 140 mg/kg) and it does not inhibit the HerG ion channel with an IC_{50} > 50 μM.

Intellectual Property

GIBH has filed intellectual property rights for composition of matter, production and medical use of D824 and related chemistry for the treatment of various cancers. Patents include 201010216603.7 and PCT/CN2011/00935.

Product

D824 belongs to a new class of anti-leukemia drugs that are active against both Bcr-Abl kinase and the T315I mutant form of the enzyme.

Indication

Primary: Chronic Myeloid Leukemia

Secondary: Solid Tumors

Design

D824 is formulated as a tablet suitable for once a day (or holiday) oral dosing.

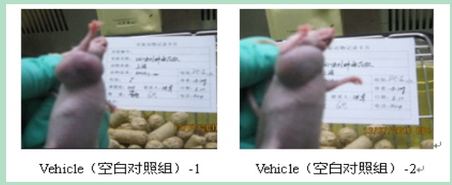
Development Status

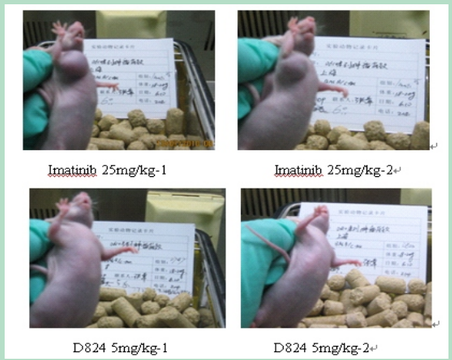
Clinical Candidate Stage: Preclinical proof-of-concept in industry-standard models of CML and solid tumors established. Safety evaluation in rodents completed. IND filing is to be initiated in 2013 for the treatment of CML.

Commercialization Strategy

Partner in China is Shunjian Pharmaceuticals, Inc. Commercial partners are being sought for development and marketing in the EU and North America.

Proof of Concept in OA rats





Anti-tumor activity of D824 in rodent xenograft model Bcr-Abl ^{T315I}.