Molecular Cancer Therapeutics

# Development of the First Generation c-Met Kinase Inhibitors: Beginning of a Path to a New Treatment for Cancer

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**Commentary on:**
Xueyan Wang, Phuong Le, Congxin Liang, Julie Chan, David Kiewlich, Todd Miller, Dave Harris, Li Sun, Audie Rice, Stefan Vasile, Robert A. Blake, Anthony R. Howlett, Neela Patel, Gerald McMahon, and Kenneth E. Lipson. **Potent and selective inhibitors of the Met [hepatocyte growth factor/scatter factor (HGF/SF) receptor] tyrosine kinase block HGF/SF-induced tumor cell growth and invasion.** Mol Cancer Ther 2003;2:1085–92.

Cloning of the *met* oncogene from chemically transformed cells was first reported in 1984 (1). Its protooncogene was subsequently reported to have the structure of a receptor tyrosine kinase (2), and its ligand was shown to be hepatocyte growth factor (HGF) in 1991 (3). By the end of 1995, when the Drug Discovery team at SUGEN decided to try to identify a small-molecule kinase inhibitor for c-Met, more than 300 articles on various aspects of c-Met biology had been published. We considered it a compelling target because activation of c-Met kinase induced important tumor responses such as angiogenesis, epithelial–mesenchymal transformation, invasion, and metastasis, and because c-Met was associated with many different types of cancer.

In early 1996, efforts began at SUGEN to develop biochemical and cellular screening assays to identify a c-Met kinase inhibitor, and we went through several iterations before we had suitable reagents for testing compounds in biochemical assays. SUGEN was a pioneer in the field of kinase inhibitors and developed tools in the early days of kinase chemistry to identify and optimize inhibitors. Molecular modeling and a targeted synthetic effort enabled us to rapidly identify the first-generation c-Met kinase inhibitors that were the subject of our original article in *Molecular Cancer Therapeutics*. The compounds described in this article had reasonable potency and good selectivity for inhibition of c-Met kinase and inhibited HGF-induced cell functions relevant for cancer. Further modification of the core scaffold led to the second generation of a c-Met kinase inhibitor, PHA-665752, which demonstrated inhibitory effects on c-Met phosphorylation and tumor growth in a xenograft model (4). Although PHA-665752 exhibited properties more suitable for use *in vivo*, these properties were inadequate for its success as a drug. This led to the decision to pursue alternative chemical scaffolds with better pharmaceutical properties. Importantly, our early c-Met inhibitors continued to serve as tool compounds for further target validation and mechanism-of-action studies in industry and academic laboratories.

The knowledge gained from our work on the pyrrolindolinone chemical series influenced the design and development of many other c-Met inhibitors, including crizotinib (PF2341066), a dual inhibitor of c-Met and anaplastic lymphoma kinases (ALK; ref. 5). Clinical trials with crizotinib started in 2006, and it received accelerated approval from the U.S. Food and Drug Administration in 2011 for treatment of a subset of patients with non–small cell lung cancer who express the abnormal ALK. Although much of the initial clinical success was observed in patients whose tumors contained ALK rearrangements (6–8), crizotinib has also demonstrated activity in a patient with a non–small cell lung cancer containing a MET amplification (9). Studies to further explore the activity of crizotinib in patient populations exhibiting dysregulated MET are ongoing. Several other c-Met kinase inhibitors are also in clinical development. It is hoped that these or other therapeutics may lead to more treatment options for cancer patients.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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