The Discovery and Development of SU14813, a Next-Generation Multitargeted Tyrosine Kinase Inhibitor for the Treatment of Human Malignancies

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SU14813 is an oral, multitargeted tyrosine kinase inhibitor (TKI) targeting vascular endothelial growth factor receptors (VEGFR), platelet-derived growth factor receptors (PDGFR), KIT, and fms-like tyrosine kinase 3 (FLT-3). These receptors play a key role in angiogenesis and the growth and metastasis of solid and hematologic tumors. SU14813 was developed as a next-generation TKI agent following sunitinib (SU11248) designed to demonstrate optimized pharmacokinetic (PK) and tolerability profiles. Sunitinib malate (SUTENT) is approved multinationally for the treatment of gastrointestinal stromal tumor (GIST) after the failure of imatinib due to resistance or intolerance, advanced renal cell carcinoma (RCC), and unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumors.

In nonclinical studies, SU14813 demonstrated broad and potent antitumor activity equivalent to that of sunitinib, which resulted in tumor regression, growth arrest, growth delay, and prolonged survival in established xenograft cancer models in mice. Importantly, there was a close correlation between the pharmacodynamic endpoints (in vivo modulation of intended targets and antitumor efficacy) and the PK of the agent. In addition, SU14813, in combination with docetaxel (DTX), improved antitumor activity compared with either single agent alone in a xenograft tumor model insensitive to DTX (1). These results led to a single-agent dose escalation phase 1 study (n = 77), where SU14813 showed manageable safety and tolerability, and a desirable PK profile under a continuous oral dosing regimen (2). The agent exhibited dose-proportional exposure with the expected target plasma concentrations achieved at doses ≥ 100 mg/day. Objective responses by RECIST including complete response (1 patient with RCC), partial responses (12), and cases of long-lasting stable disease were observed.

In a dose-range finding combination study in patients with advanced solid tumors (n = 24), continuous daily dosing of SU14813 (50 mg/day) plus sub-MTD dose of DTX (75 mg/m²) was identified to be a manageable and potentially active combination regimen (3). Grade 3-4 toxicities observed were similar to those from single-agent DTX and there was no clinically relevant drug–drug interaction in PK. The combination therapy demonstrated encouraging clinical activity in several heavily previously-treated patients with melanoma and in patients with GIST who were previously refractory to imatinib and/or sunitinib.

In summary, SU14813 appears to be an active and well-tolerated next generation multitargeted TKI and may be used as a single agent or in combination with cytotoxic or tumor-targeting agents for the treatment of human cancers.

Disclosure of Potential Conflicts of Interest

D. Hu-Lowe, N. Brega, and S. Patyna are employees of Pfizer Inc. and own Pfizer stock.

Received September 13, 2011; accepted September 21, 2011; published November 9, 2011.

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Molecular Cancer Therapeutics

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