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12:00 NOON, CONFERENCE ROOM 323A

Discovery of 4-Amino-3-benzimidazol-2-yl-hydroquinolin-2-ones as Multiple Receptor Tyrosine Kinase Inhibitors for the Treatment of Renal Cell Carcinoma

Renal cell carcinoma is a highly vascularized tumor, which is dependent upon the angiogenic pathway for growth and survival. Until recently, the mainstay of treatment was cytokines therapy with little benefit in terms of progression-free survival (PFS) and overall survival (OS). Since 2005, many new agents have been approved by FDA for the treatment of locally advanced or metastatic renal cell carcinoma (mRCC) with substantial improvement in the overall survival OS. The majority of these drugs are targeting VEGF (vascular endothelial growth factor) or mTOR (mammalian target of rapamycin) pathways.

Although targeting mTOR or VEGF pathways represents the standard care in patient with mRCC, resistance usually developed after a median of 6–15 months of treatment. Therefore, there is a medical need for targeting other receptors as a therapeutic strategy for treatment of mRCC. One of the new pathways being targeted for treatment of mRCC is the fibroblast growth factor (FGF) pathway. Fibroblast growth factor (FGF) pathway activation induces angiogenesis in the early invasive phase and late vascular maturation phase, and it has been proposed as a mechanism of anti-VEGF escape. The increase in FGF2 plasma level in patients with progressive RCC while they were receiving anti-VEGF- therapies or previously received anti-VEGF-therapies revealed the importance of FGF pathway inhibition for targeting anti-VEGF escape. High-throughput screening, hit-to-lead optimization, biochemical assays, cell-based assays, in vivo studies, led to a successful discovery of Dovitinib (TKI258) by Novartis Pharmaceuticals. Dovitinib, is a potent (EC50 value ~ 0.1 μM), an orally efficacious tyrosine-kinase inhibitor that inhibits VEGFR, PDGFR (platelet-derived growth factor receptor), and FGFR. Based on its favorable in vitro drug-like properties (potency, solubility, and drug-drug interactions) and in vivo potency, Dovitinib was selected for further clinical evaluation and is currently in phase III clinical trials.

References:

