ESTABLISHMENT OF THE ORTHOTOPIC PRIMARY HUMAN HEPATOCELLULAR CARCINOMA MODEL FOR ONCOLOGY DRUG DISCOVERY

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Introduction: Hepatocellular carcinoma (HCC) is the most common liver malignancy, and the third most common cause of cancer-related mortalities worldwide. Most cases occur in Asia, and in China alone an estimated 251,000 male and 95,000 female patients are diagnosed annually. Although significant advances have been made with the use of certain chemotherapeutic and targeted therapeutic agents in HCC treatment, the prognosis for most liver cancer patients remains poor. Pfizer Oncology has significantly strengthened its research and drug discovery activities targeting HCC. As part of the effort, we have developed series of animal models that are instrumental in target validation, efficacy screening and translation research.

Methods: Tumor fragments derived from patient tumor tissues were surgically implanted into the left lobe of nude mouse liver. Tumor-bearing mice were treated with sunitinib malate (Sutent) or vehicle control from day 7 post implantation for 3 weeks. Plasma samples were collected at different time points for alpha-feto-protein (AFP) measurement. At termination, tumors were excised from liver and their weights and sizes were recorded.

Results: Sutent was well tolerated in the animals during the course of the study. Sutent treatment significantly inhibited orthotopic HCC tumor growth measured by size, weight and circulating AFP. In addition, histological analysis confirmed that orthotopically implanted primary human tumors maintained their histopathological characteristics.

Conclusions: The initial results indicate that this model can better reflect human disease by preserving heterotypic nature of tumor cells and stroma, and by maintaining tissue-specific histopathology and by retaining particular genetic mutations, pathogens and disease markers that are naturally associated with clinical disease, and therefore can serve as a valuable tool for target validation, efficacy study, as well as patient population selection.