Introduction

- FGFR receptor signaling plays a role in cell proliferation, differentiation, survival, angiogenesis and regulation of vitamin D and phosphate homeostasis.
- aberrant activation of the FGFR pathway has been shown to promote tumorigenesis and angiogenesis across multiple cancer indications.
- FGFR amplifications are frequently found in breast, gastric, ovarian, urothelial, colorectal and other squamous cancer.
- FGFR diversity has hampered the development of effective FGFR pathway inhibitors due to the need to block the activation of multiple receptors.

Introduction

MM-161 is an Active Ligand Blocker and Inhibits Downstream Activation of pERK

- MM-161 Inhibits Tumor Growth in Xenograft Models by Two Independent Mechanisms of Action
  - MM-161 blocks binding of FGFR ligand to the FGFR receptors.
  - MM-161 shows comparable activity to a pan-FGFR TKI (BGJ398) as measured by pERK inhibition (SureFire pERK).

Targeting of Multiple FGF Receptors is Required for Maximal Growth Inhibition In Vitro

- Inhibition of individual FGFRs shows limited effect on cell viability, even in clearly FGFR1 driven cell lines.
- MM-161, a pan-FGFR inhibitor, shows superior activity inhibiting cell viability regardless of receptor expression profile.

MM-161 Design

- Antibody designed to block ligand binding to c-isoform FGFRs
- Offers greater specificity than small molecule FGF pathway inhibitors
- MM-161 is a potent inhibitor of the FGF pathway activation in preclinical models of lung, renal, breast, ovarian and other cancers

MM-161 is Well Tolerated in Animal Models

- Sun et al. previously reported that systemic delivery of the antagonist FGFR1 antibody caused potent but reversible hypophagia and weight loss in rodents and monkeys. Here we generated MM-161 molecules with various levels of effector function:
  - full (+ Eff-ƒ)
  - partial (+/- Eff-ƒ)
  - no (- Eff-ƒ)
- MM-161 with full or partial effector function cause substantial weight loss within 2 days of the first dose. Importantly the effector less lead molecule does not affect food intake and weight stays stable even at high doses of 20mg/kg.

Summary

- MM-161 is well tolerated in mice and cynomolgus monkeys with no significant weight loss observed in either species.
- MM-161 does not cause hypoglycemia or hyperphosphatemia in mice or cynomolgus monkeys.
- MM-161 monotherapy leads to significant tumor growth inhibition or tumor regression of xenografts of human lung, renal and endometrial cancer amongst others.
- MM-161 has a dual mechanism of action by inhibiting both proliferation and angiogenesis.
- Taken together, our preclinical data strongly supports the clinical evaluation of MM-161 in cancer patients.