**Combination of Imatinib Mesylate with AKT inhibitor (miransertib, ARQ 751) or FGFR inhibitor (derazantinib) show synergy in GIST cell lines and preclinical models**

Marya Kozinova1, Shalina Joshi1, Phillip Zook1, Jimson D.Souza1, Jeffrey M. Farma1, Nestor Esnaola1, Sanjay Reddy1, Karthik Devrajan1, Reza Foroughi1, Yi Yu1, Brian Schwartz2, Terence Hal1, Margaret von Mehren1, and Lori Rink1

1 Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA; 2 ArQule Inc., Burlington, Massachusetts, USA

**Abstract**

The majority of gastrointestinal stromal tumors (GIST) harbor oncogenic mutations in the receptor tyrosine kinase KIT or platelet-derived growth factor receptor alpha (PDGFRα). Small molecule kinase inhibitors such as imatinib mesylate (IM) have significantly improved the clinical management of GIST by targeting these mutant receptors. Despite strong overall response rates to IM, disease progression generally occurs in time. Inhibiting targets other than, or in addition to, KIT/PDGFRα may provide additional therapeutic benefit in GIST. Both AKT and FGFR signaling have recently been reported to be resistance mechanisms associated with drug resistance in GIST cell lines and tumors. In this study, we performed in vitro and in vivo experiments to assess the potential benefit of combining IM with the following ArQule AKT inhibitors, ARQ 092 (miransertib) and ARQ 751 and FGFR inhibitor, ARQ 087 (derazantinib). To evaluate in vitro drug sensitivity, a panel of IM-sensitive (GIST-T1; GIST882) and resistant GIST cell lines (GIST-T1;GIST829, GIST430) were subjected to drug treatment for 72 hours before measuring viability with the Cell Titer Blue Viability Assay. Synergy between IM and ARQ 092, ARQ 751 and ARQ 087 was quantified using the Chou-Talalay algorithm to calculate CI values. CI values <1 are considered synergistic. The 3:1 molar ratio of the three tested combinations demonstrated synergistic CI values in all four GIST lines. Immunoblot assays confirmed that drugs hit their intended targets in each cell line following six-hour drug treatment. Interestingly, a significant decrease in the activation of a downstream signaling protein, p-AKT, was observed with ARQ 092, ARQ 751 and ARQ 087 as monotherapies and in combination with IM. These results demonstrate that IM in combination with the novel ArQule AKT inhibitors (ARQ 092 and ARQ 751) and FGFR inhibitor (ARQ 087) provided significantly improved efficacy compared to monotherapy. These results provide justification for development of studies evaluating these combinations in GIST patients.

**Response markers: ARQ 092 / IM**

**ARQ 092, ARQ 751 and ARQ 087 have synergistic effects in combination with IM on in vitro GIST cell growth**

**Conclusions and future directions**

- Several molar ratios of the combinations were tested. The 3:1 (ARQ-IM) molar ratio was synergistic across all four GIST cell lines consistent with our previous data for MK-2206 and IM combination.
- Treatment with the three combinations resulted in enhanced sensitivity to the drugs in IM-resistant GIST cell lines (GIST430, GIST-T1;GIST829).
- In vitro studies demonstrating drug synergy between these inhibitors and IM at a 3:1 molar ratio in a panel of IM-sensitive and - resistant GIST cell lines.
- IM in combination with miransertib, ARQ 751 or derazantinib provided significantly improved efficacy compared to monotherapy in both IM-sensitive and resistant in vivo xenograft models of GIST.
- These results provide justification for development of studies evaluating these combinations in GIST patients.