CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
DP150127

Project Title:
Engineered AXL Decoy Receptor for Treatment of AML & Solid Tumors

Award Mechanism:
New Company Product Development Award

Principal Investigator:
Giaccia, Amato

Entity:
Ruga Corporation

Lay Summary:

Ruga Corporation is a late preclinical stage pharmaceutical company developing Ruga-S6, an engineered decoy soluble AXL receptor, for targeted therapy against acute myeloid lymphoma (AML) and certain solid tumor indications including ovarian, pancreatic, and breast cancer.

AML is a hematologic cancer affecting both pediatric and adult patients. While the pediatric population is small (~800), over 18,000 adults are diagnosed in the US annually, with the majority of these patients over 65. Based on 1996-2002 SEER statistics, the 5-year survival rate for adults older than 65 diagnosed with AML was a mere 4.3%. In the past 20 years, there has been little improvement in overall survival for AML patients particularly those older and with unfavorable cytogenetics like FLT3-ITD mutations (~20-25% of AML patients). Older AML patients are more likely to experience treatment-related toxicity and less likely to achieve complete remission and remain relapse-free. As such, an efficacious drug without significant risk of toxicity is a major unmet clinical need in this underserved population.

Research indicates that activation of the GAS6-AXL signaling pathway acts as a “survival switch” required for adaptation of tumors for increased in vivo tumor growth, survival, and metastasis as well as development of resistance to commonly-used chemotherapeutic agents. Ruga-S6 is a novel Fc-fusion protein that potently neutralizes GAS6 and effectively “turns off” AXL signaling in tumor cells. It shows >100 fold tighter affinity for GAS6 and provides significantly higher specificity for the AXL/GAS6 pathway that other kinase inhibitors (e.g. small molecules and antibodies) cannot match. Ruga-S6’s neutralization of GAS6 and inhibition of AXL-GAS6 pathway offers the potential for a novel, targeted therapeutic approach that may be used alone with low toxicity or in?combination with other standard of care anti-cancer agents.

Ruga-S6 has the potential to impact the current standard of care for FLT3-ITD(+) AML by inhibiting activation of AXL/GAS6 signaling, which is correlated with increased clinical rates of metastasis, progression, recurrence, and overall poorer survival in AML and other cancers. It offers a more targeted therapy, with minimal systemic toxicity and less severe side effects than current AML chemotherapeutics. Ruga-S6 could also be delivered as a combination therapy for AML with approved chemotherapeutic agents such as cytarabine. While AML is planned as the initial target indication for Ruga-S6, Ruga has built a compelling rationale to pursue certain solid tumors in the clinic such as ovarian,

renal, breast, lung, and pancreatic cancers. In solid tumors, AXL/GAS6 inhibition has shown to have dual anti-cancer effects, including direct anti-tumor effects on survival, invasion, and chemo-resistance, and also indirect anti-tumor effects via stimulating innate anti-cancer immunity, given GAS6 role as an innate immunity check point.
To date, Ruga has conducted several preclinical proof-of-principle studies and established compelling data demonstrating Ruga-S6's efficacy and tolerability in multiple in vitro studies and in vivo models of cancer. In preclinical models of AML, including patient-derived leukemic cells from FLT3-ITD(+) patients, treatment with Ruga-S6 has been associated with remarkable anti-tumor effects coupled with exceptional tolerability, making Ruga-S6 a potentially ideal drug for AML patients. In preclinical models of advanced, drug resistant ovarian cancer, the treatment with Ruga-S6 lead to greater than 95% of animals to become disease free without any tolerability issues. Preclinical studies in breast, lung, renal and pancreatic cancer models generated equally compelling data. Furthermore, Ruga has developed a proprietary companion diagnostic assay for the measurement of free and total GAS-6 levels, which provides for the identification of patients that could preferentially benefit from therapy with Ruga-S6.

In order to advance to commercial development, Ruga has developed a comprehensive plan to complete the manufacturing, preclinical, and clinical development necessary to seek approval of Ruga-S6 with the US Food and Drug Administration (FDA). Preclinical toxicology, immunogenicity, and biomarker studies will position Ruga for filing for an Investigational New Drug (IND) application by Q1 2017. Ruga will then commence Phase 1/2 clinical studies, which will include parallel Phase 1a multiple ascending dose studies for enriched AML and specific solid tumor indications. Lastly, phase 1b/2a studies will be performed as a multiple dose study in selected patient populations expanded from completion of the Phase 1a studies. In total, these studies are anticipated to provide sufficient evidence for Ruga-S6 to pursue both FDA Orphan Drug and Breakthrough designation, and further, to validate the use of Ruga's companion diagnostic for stratification of patients for targeted therapy with Ruga-S6.