First-in-human study with ARQ 092, a novel pan AKT-inhibitor, in subjects with advanced solid tumors or recurrent malignant lymphoma

Mansoor Saleh1, Kyri Papadopoulos2, Alireza Arabnia1, Amita Pathak3, Robin M. Stein1, Feng Chai3, Maria Lamar3, Ron Savage3, Giovanni Abbabessa3, Anthony Tolcher2

1. Georgia Cancer Specialist Affiliated with Northside Hospital Cancer Institute, Atlanta, GA, USA; 2. START, San Antonio, TX, USA; 3. ArQule, Inc.; 19 Presidential Way, Woburn, MA 01801

BACKGROUND

• AKT signal pathway is abnormally dysregulated in a wide range of tumor types.
• Extensive molecular evidence validates the pathway as a target in cancer.
• ARQ 092 is an oral, allosteric, ATP-independent, potent and selective AKT inhibitor that binds to the pleckstrin homology domain, preventing ATP from being allosterically activated.

STUDY DESIGN AND METHODS

Objectives

Primary: Safety and tolerability in subjects with cancers
Secondary: Pharmacokinetic profile; pharmacodynamic activity; MTD and RP2D; preliminary evidence of activity

Exploratory: Association between markers of the AKT signaling pathway, toxicity and clinical activity; changes in different pathways and prediction of potential combinations

Key inclusion criteria

Histologically/ cytologically documented advanced/metastatic solid tumors or recurrent malignant lymphoma in subjects who failed standard therapy; ECOG PS 0-2; evaluable or measurable disease per RECIST 1.1 or Revised Response Criteria for Malignant Lymphoma, adequate organ function

Key exclusion criteria

History of 1 or 2 diabetes mellitus requiring regular medication (other than metformin or other oral drugs); hypothyroidism or hypertension controlled < 24 weeks prior to dose
diabetic nephropathy, severe hyperlipidemia, unstable diabetes mellitus, patients with severe or uncontrolled conditions of any kind

Study design

Open-label, phase 1 dose escalation study; 3+3 subjects per cohort (‘Y ELT’); expansion cohort of up to 40 subjects at MTD/RP2D; a food-effects cohort at MTD of weekly schedule

DLT (occurrence within the first treatment cycle [4 weeks])

Standard DLT criteria; Grade 3 or asymptomatic Grade 4 hyperglycemia not improving to < 250 mg/dL despite appropriate treatment for 1 week or asymptomatic Grade 4 hyperglycemia (> 500 mg/dL)

MTD

Dose level at which ≤ 1 of 8 subjects experienced DLT

Drug administration and dosing schedule

Capsules were administered orally without food (except food-effect cohort).

Dosing schedule

MTD: 250 mg BID, QW
RP2D: 300 mg BID, QD

RESULTS

• Preliminary signals of single agent activity in subjects with advanced tumors have been observed.
• p-AKT, t-PRAS40 and p-PRAS40 expression levels in tumor tissue from one subject with uterine sarcoma decreased after treatment with ARQ 092.

CONCLUSIONS

• ARQ 092 has a safety profile predicted by preclinical models and in line with other AKT inhibitors. Its toxicities are manageable in cancer subjects.
• MTDs for all three dosing schedules have been reached.
• Drug exposure increases in a dose-dependent fashion with median T_{max} range from 4.4-6 hours, mean half-life range from 19-53 hours and an accumulation ratio range of 3.0-2.5.
• ARQ 092 has a manageable PK profile with a slowly decreasing C0 half-life. A non-linear relationship between plasma ARQ 092 and plasma p-AKT was observed.

Preliminary signals of single agent activity in subjects with advanced tumors has been observed including 1 PR in a heavily pretreated lymphoma subject.

 Expansion of RP2D is ongoing to enroll subjects with advanced, lymphoma and other tumor types with AKT-2 or 3 mutation or amplification.

Poster presented at EORTC/NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, 19-21 November 2017, Barcelona, Spain.