Exploratory Study on Predictive Biomarkers for ARQ 092, a Novel Selective pan-AKT Inhibitor

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BACKGROUND

AKT is a well-characterized kinase and a critical component mediating the PI3K-AKT signaling pathway. It plays an important role in cell cycle progression, survival, proliferation and growth. Hyperactivation of the PI3K-AKT signaling pathway has become a novel strategy against cancer. AKT can be constitutively activated through altered membrane receptor kinases, gain-of-function mutations of PIK3CA, PIK3R1, PTEN loss-of-function or over-expression. As a tumor suppressor, E-cadherin encoded by CDH1 gene and its paralogs contribute to epithelial-mesenchymal transition and metastasis in cells. Therefore, AKT and E-cadherin are regarded as the target for PI3K-AKT and CDH1 pathway respectively. In this study, we demonstrate that ARQ 092 inhibits Akt phosphorylation AKT and its downstream phosphorylation (pPRAS40, pPRAS58, pPRAS60), respectively. Significant inhibition of pAKT and pPRAS were also observed in ARQ-CA-knockdown model. In an in vitro assay study with ARQ 092, PIK3CA mutation was tested in the study as well. Furthermore, we have validated the low expression mutation of PI3K gene encoding E-cadherin is associated with ARQ 092 sensitivity in vitro cell lines. Thus, ARQ 092 was chosen to suppress a large panel of cancer cell lines, particularly breast cancer, leukemia and CRC. Mutant analysis indicates that gene inactivation of PI3K or AKT pathway by ARQ 092 may result from the combination of ARQ 092 and its target therapy. Our analysis also suggests that a breast cancer patients may respond to a targeted indication for ARQ 092.

MATERIALS AND METHODS

Cell panel

ARQ-CA, PIK3CA/R1 and CDH1 mutation independently predict the response of ARQ 092 treatment

Breast cancer, leukemia, and CRC are among the most sensitive cancer types

Results

Cellular Pharmacodynamic Effect

ARQ 092 Inhibits AKT Activation

ARQ 092 was concentrated with 10% DMSO and 1% DMSO supplemented with 10% FBS maintained at 37°C in a humidified atmosphere at 5% CO2

In vitro proliferative assay

ARQ 092 was included in triplicate with 10% DMSO for 72h and 96h before staining

Antiproliferative Effect of ARQ 092 on Human Cancer Cell Lines

ARQ 092 was included in triplicate with 10% DMSO for 72h and 96h before staining

CONCLUSIONS

1. PIK3CA/R1 and CDH1 mutation independently predict the response of ARQ 092 treatment
2. PTEN status may not play a significant role on ARQ 092 sensitivity
3. Breast cancer, leukemia, and CRC are among the most ARQ 092-sensitive cancer types