Development and validation of a pharmacodynamic (PD) assay for TOS-358, the first covalent inhibitor of PI3Kα in clinical development

Author Block:
John R. MacDougall, John Bradley, Neil Dhawan, Wei Chen.
Totus Medicines Inc., Emeryville, CA

Abstract:
TOS-358 is a first-in-class covalent inhibitor of PI3Kα and is currently in clinical development in a variety of solid malignancies. We have developed a fit-for-purpose pharmacodynamic assay to evaluate the target occupancy of TOS-358 in in vitro and in vivo setting at multiple timepoints.

The PI3Kα assay allows direct measurement of both occupied and total protein in multiple different samples and tissue types. Signals of occupied and unoccupied PI3Kα proteins can be readily measured in cellular and in vivo samples. The assay was utilized in a large panel of cancer cell lines, revealing a direct correlation between target occupancy and pathway inhibition of markers such as phosphoAKT and phosphoS6.

Critically, these correlations revealed the need to achieve near complete suppression of PI3Kα to enable sustained pathway inhibition and cancer cell death. We furthermore utilized this assay to explore the turnover rate of PI3Kα across multiple diverse tumor types, mutations, and tissues. This approach enables highly sensitive target engagement analysis of TOS-358 across multiple formats.