Pediatric Preclinical Testing Program (PPTP): Evaluation of the MEK1/2 Inhibitor AZD6244 against Juvenile Pilocytic Astrocytoma (JPA) Xenografts

Malcolm A. Smith1, Christopher Morton2, Doris Phelps2, Geoffrey A. Neale2, Peter J. Houghton3. 1 CTEP/NCI, 2 St. Jude Children’s Research Hospital, 3 Nationwide Children’s Hospital

Background

AZD6244 (ARRY-142886) is a potent, highly specific small molecule inhibitor of MEK1/2 that is not competitive with ATP.

In Stage 1 testing of AZD6244 against the PPTP in vitro panel:
- Growth inhibition was observed in a minority of the 23 PPTP cell lines.
- Kasumi-1, a cell line with an activating KIT mutation, was the most responsive cell line and the only cell line with a clear cytotoxic response to AZD6244.

In Stage 1 testing of AZD6244 against the PPTP in vivo tumor panels, the following was observed:
- AZD6244 induced significant differences in EFS distribution in 10 of 37 (27%) solid tumor models and 0 of 6 acute lymphoblastic leukemia (ALL) models.
- No objective responses were observed.

Recent reports describing molecular characterization of juvenile pilocytic astrocytomas (JPAs) has shown tandem duplication producing a novel fusion gene (KIAA1549-BRAF) that lacks the BRAF regulatory domain and leads to constitutive activation of BRAF.

Activating point mutations in BRAF are less frequent in JPA, accounting for only 5 percent of cases.

AZD6244 was evaluated against two JPA xenografts, BT-35 and BT-40, that are used for secondary testing by the PPTP.

AZD6244 was highly active against the BT-40 JPA xenograft that harbors constitutively activated BRAF as a result of a V600E mutation.

AZD6244 was inactive against BT-35, which has wildtype BRAF, just as it was against most of the PPTP Stage 1 xenograft panels.

AZD6244 blocks MAPK pathway signaling at the 100 mg/kg dose that is effective against BT-40.

The BT-40 xenograft model may be valuable for developing rational combinations of molecularly-targeted agents against JPAs with BRAF activation.

The complete regressions induced by AZD6244 against a BRAF-mutant pilocytic astrocytoma are a strong activity signal pointing to the potential utility of MEK inhibition for this tumor type.

Further dose-response testing will provide insight into whether tumor regressions for BT-40 can occur at doses that produce drug exposures achievable in the clinical setting.