Pediatric Preclinical Testing Program (PPTP) evaluation of the Akt inhibitor GSK690693

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Abstract

GSK690693 is a potent, selective, ATP-competitive pan-AKT kinase inhibitor. The PPTP includes an in vivo testing set to evaluate GSK690693 against 27 in vitro cell lines and 4 xenografts. A subcellular fraction of cell lines was treated with 3-5 x 10^6 GSK690693. GSK690693 had a median IC50 of 3.8 nM for the entire panel of 1.2 µM with the most sensitive cell line being the T-cell ALL cell line COG-LL-217 which had an IC50 of 6 nM.

GSK690693 was most active against the cell lines of the ALL panel and was least active against cell lines from the neuroblastoma panel. In vitro cell lines showed IC50 values of approximately 100 nM or lower and also demonstrated a strong cytotoxic response to GSK690693, whereas another 5 cell lines failed to achieve their IC50 at the highest concentration tested (10 µM).

In vitro sensitivity of three T-cell ALL xenografts (ALL-5, orange, ALL-16, red and ALL-31a, black) after 48 hours GSK690693 exposure in an MTT assay.

In vivo sensitivity of six B-lineage ALL xenografts (ALL-2, green, ALL-15 yellow, ALL-4, light blue, ALL-7, dark blue, ALL-17, purple and ALL-15 red) after 48 hours GSK690693 exposure in an MTT assay.

Conclusions

GSK690693 was most active in vitro against the cell lines of the ALL panel and was least active against cell lines from the neuroblastoma panel. In vitro testing using short term culture of ALL xenografts showed lower levels of activity for GSK690693 compared to the level of activity observed for ALL cell lines. GSK690693 was adequately tolerated (toxicity in ~10% of treated animals) at the dose / schedule tested (30 mg/kg daily x 5 repeated for 6 weeks).

GSK690693 showed limited activity against the xenografts of the PPTP in vivo.

- Significant differences in EFS distribution were observed for 6 of the 8 osteosarcoma xenografts and 2 of the xenografts from the glioblastoma panel.
- Two xenografts showed EFS T/C values > 2.
- Significant differences in EFS distribution were observed for 6 of 6 of the osteosarcoma xenografts. 30 mg/kg GSK690693 in vivo was tested.

- Pharmacodynamic effects:
  - Pharmacodynamic effects of GSK690693 were evaluated following a single dose of 10 or 60 mg/kg for the osteosarcoma xenograft OS-33. The expected upregulation of pAKT (Ser 473) was noted.
  - GSK690693-induced reductions in pGSK occurred at 1 hr post dosing with recovery by 6 hr.

- Pharmacodynamic effects or combination with other signaling inhibitors may enhance the activity of GSK690693 against pediatric preclinical models.