Abstract C106
Pediatric Preclinical Testing Program (PPTP) Stage 1 evaluation of the PI3K inhibitor XL147 (SAR245408)

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XL147 (SAR245408) IN VITRO ACTIVITY

The median relative IC50 (%IC50) for XL147 against the PPTP cell lines was 19.3 µM, (range 2.7 µM - 24.5 µM).

There was a trend for lower values for the rhabdomyosarcoma XL147 induced Ymin values approaching 0% for PPTP cell lines.

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shows strong tumor growth inhibition as a single agent in multiple adult cancer xenograft tumor models associated with increased apoptosis and inhibition of tumor angiogenesis.

Currently in adult phase 2 trials (single agent) and in trials in combination with chemotherapeutic and targeted agents.

In vivo: Testing was for 96 hours at concentrations from 1.0 nM to 10.0 µM with weekly calibrations.

XL147 was well tolerated at 100 mg/kg administered orally for 14 consecutive days.

XL147 inhibited tumor growth in most PPTP solid tumor xenografts as shown by significant differences in EFS distribution compared to control in 26 of 30 (87%) evaluable solid tumor xenografts. Two of 7 (29%) evaluable ALL xenografts showed significant differences in EFS distribution.

Three of 28 (10%) evaluable solid tumor xenografts met criteria for intermediate EFS TIC activity (EFS TIC>0): 2 of 6 rhabdomyosarcoma and 1 of 5 neuroblastoma. Objective responses (PR/CR) were not observed.

Baseline levels of PI3K activation, as assessed by phospho-AKT levels, did not appear related to in vivo response to XL147.

Under the conditions evaluated in this study, XL147 achieved modest single-agent activity against the PPTP preclinical models.

Genomic activation of PI3K signaling (e.g., through PIK3CA mutation or PTEN deletion) appears relatively uncommon in pediatric solid tumors compared to adult cancers, which may contribute to the limited single agent XL147 activity observed.

Preclinical evaluations of XL147 in combination with particular standard agents and with other pathway signaling inhibitors are planned.