#5265 Pediatric Preclinical Testing Program (PPTP) Stage 1 Evaluation of BMS-754807 IGF-1R Receptor Inhibitor

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Abstract

In vivo - in vitro testing was performed using DBMSCAN, a xenograft model, to determine whether the activity observed in vitro (using fluorescent dye (PDAC) cell numbers in tissue culture and cell kill assays) translates to activity in vivo (2 of 6 xenograft lines in the Wilms panel inhibited by BMS-754807 and the toxic effects that have enter phase 1 clinical trials.

Results: The BMS-754807 IC50 value for the IC50 cell lines was compared to that of a murine monoclonal antibody (mAb391) directed against the human IGF-1R. Significant differences in ETS distribution compared to controls in 10 of 12 evaluable xenografts were observed. Criteria for intermediate activity for the time to event activity measure (EFS T/C > 2) were met in 7 of 27 solid tumor xenografts and were most commonly observed in the neuroblastoma (3 of 6) and rhabdomyosarcoma (2 of 6) panels. Objective responses (i.e., tumor regression) were not observed in 27 solid tumor xenografts and were most commonly observed in the neuroblastoma (3 of 6) and rhabdomyosarcoma (2 of 6) panels.

Conclusions: BMS-754807 showed broad tumor growth inhibition activity against the PPTP in vitro panel xenografts. Future studies will focus on defining how pharmacokinetic and pharmacodynamic parameters impact in vivo activity.

Background:
Signaling through the type 1 insulin-like growth factor receptor (IGF-1R) is involved in a number of essential physiological processes including growth, development, and metabolism. Overexpression or hyperactivation of IGF-1R has been associated with the growth of many malignancies and is a major target in cancer therapy. Combinatorial small molecule inhibitors of IGF-1R and the insulin receptor that enter phase 1 clinical trials.

Methods:
The PPTP includes a xenograft panel (in vivo panel) and a cell line panel (in vitro panel) and in vivo xenografts were inoculated with the anti-IGF-1R antibody mAb391 (8 x 106). In vivo testing used a dose of 25 mg/kg BMS-754807 administered daily x 5 to 6 weeks and growth, in vivo antitumor activity was measured using a time to event measure based on the median EFS of treated and control lines (intermediate EFS T/C activity was most commonly observed in 7 of 27 solid tumor xenografts). Assuming tumors to be spherical, volumes were calculated from the formula (4/3) pi x r3. Shading in the EFS columns indicates xenografts that have either high (dark blue), intermediate (light blue) or low (white) EFS T/C between treated and control groups.

RESULTS AND CONCLUSIONS

The median EC50 for the in vitro panel was 0.62 µM. There was >70-fold range in EC50 values, with the most sensitive cell line being the rhabdomyosarcoma cell line Rh14 (EC50, 0.07 µM) and the least sensitive cell line being Rh18 (EC50, 4.96 µM).

The median EC50 for the 4 Ewing sarcoma cell lines was less than that for the remaining 19 cell lines (0.19 µM versus 0.78 µM, p=0.047).

BMS-754807 was provided for testing by Bristol-Myers Squibb.

BMS-754807 IN VITRO ACTIVITY

The median EC50 value for BMS-754807 for the 5 cell lines with the greatest response to the anti-IGF-1R monoclonal antibody mAb391 (highlighted in red bars in the figure) was 0.12 µM. The median EC50 for the 10 cell lines with the least evidence of mAb391 treatment effect was approximately 10-fold higher at 1.5 µM (p=0.0017).

The observation is consistent with a specific IGF-1R for BMS-754807 that has half-maximal responses to approximately 1 µM. This suggests that this agent may be effective for selected pediatric cancers. Combinations targeting multiple, related signaling pathways warrant evaluation.

BMS-754807 was tested against the PPTP in vitro panel xenografts and were most commonly observed in the neuroblastoma (3 of 6) and rhabdomyosarcoma panels (2 of 6). Single xenografts in the Wilms tumor and Ewing sarcoma panels also showed intermediate activity.

The broad activity of BMS-754807 in pediatric sarcomas and neuroblastoma xenografts suggests that this agent may be effective for selected pediatric cancers. Combinations targeting multiple, related signaling pathways warrant evaluation.

- BMS-754807 was evaluated in 45 xenograft models at 25 mg/kg BID using a 6 days per week x 6 weeks schedule. BMS-754807 was tolerated at this dose, with mortality for treated animals 6.5%.
- BMS-754807 showed significant differences in EFS distribution compared to controls in 18 of 32 evaluable solid tumor xenografts (56%). The tested ALL xenografts did not show significant treatment effects to BMS-754807.
- Objective responses were not observed for any solid tumor and ALL xenografts.
- Criteria for intermediate activity for the time to event activity measure (EFS T/C > 2) were met in 7 of 27 (26%) evaluable solid tumor xenografts.

Intermediate EFS T/C activity was most commonly observed in the neuroblastoma (3 of 6) and rhabdomyosarcoma panels (2 of 6). Single xenografts in the Wilms tumor and Ewing sarcoma panels also showed intermediate activity.