Pediatric Preclinical Testing Program (PPTP) evaluation of the
MEK1/2 inhibitor AZD6244 (ARRY-142886)


Abstract

Background: AZD6244 is a potent, selective and pan-pancreatic inhibitor of MEK1 and MEK2 currently in phase 2 clinical development. The activity of AZD6244 was evaluated against the PPTP in vivo xenograft panel. AZD6244 was provided to the PPTP by AstraZeneca. Testing was supported by NCI NO1CM42216.

Objectives: To evaluate in vivo activity of AZD6244 against the MEK signaling pathway in a variety of xenograft models using both naive and genetically engineered models of cancer.

Methods: AZD6244 was provided to the Pediatric Preclinical Testing Program by AstraZeneca through the Cancer Therapy Evaluation Program (NCI). AZD6244 was administered to a minimum of 5 tumor xenografts from each solid tumor panel and in one-half of the xenografts from the osteosarcoma panel (3 of 6).

Results: The best in vivo activity was observed in the glioblastoma panel (3 of 4) and in one-half of the xenografts from the osteosarcoma panel (3 of 6). AZD6244 was provided to the PPTP by AstraZeneca. Testing was supported by NCI NO1CM42216.

In Vitro Test Results for AZD6244

In vitro activity was observed in a minority of the 22 cell lines tested. AZD6244 was provided to the PPTP by AstraZeneca. Testing was supported by NCI NO1CM42216.

Conclusions: AZD6244 was highly active against AZD6244 in vivo with an activating KIT mutation, but was active against the majority of the cell lines in vivo with human cancer xenografts. These results suggest a potential role for AZD6244 in the treatment of human cancer in vivo.

Methods for PPTP In Vivo Testing

In Vivo Testing

AZD6244 in vivo activity was most pronounced for Kasumi-1, an AML cell line with an activating KIT mutation. The response of Kasumi-1 to AZD6244 is similar to that previously described for Kasumi-1 against S-Ref and Flak mutant cell lines. Other PPTP cell lines showed responses to AZD6244.

AZD6244 was well tolerated at the dose and schedule used for in vivo testing.

Online differences in EPS distributions in the glioblastoma panel (3 of 4) and in one-half of the xenografts from the osteosarcoma panel (3 of 6), but not in none of the evaluable xenografts in the Ewing, Wilms, neuroblastomas, and ALL panels.

AZD6244 did not induce objective responses in any of the solid tumor panels or in the ALL panel. The best response to AZD6244 was PD2 (progressive disease with growth delay), with PD2 activity concentrated in the glioblastoma panel (2 of 4) and the osteosarcoma panel (3 of 6).

Constitutive phosphorylation of ERK was documented in the PPTP osteosarcoma xenografts (data not shown), indicating baseline MEK activation for the xenografts.

Potential areas of future focus in PPTP evaluations of AZD6244 include:

- Documenting the extent and duration of MEK inhibition at the doses/exposure evaluated for efficacy testing.
- Evaluating selected combinations of AZD6244 with other signal transduction inhibitors (e.g., rapamycin).

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AZD6244 In vivo Activity

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Table: AZD6244 in Vivo Activity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tumor Panel</th>
<th>EFS</th>
<th>Tumor Volume</th>
<th>Actual</th>
<th>P-Value</th>
<th>Heat Map</th>
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<tr>
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<tr>
<td></td>
<td>Glioblastoma</td>
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CONCLUSIONS

AZD6244 in vitro activity was most pronounced for Kasumi-1, an AML cell line with an activating KIT mutation. The response of Kasumi-1 to AZD6244 is similar to that previously described for Kasumi-1 against S-Ref and Flak mutant cell lines. Other PPTP cell lines showed responses to AZD6244.

AZD6244 was well tolerated at the dose and schedule used for in vivo testing.

Significant differences in EPS distribution occurred in the majority of xenografts in the glioblastoma panel (3 of 4) and in one-half of the xenografts from the osteosarcoma panel (3 of 6), but not in none of the evaluable xenografts in the Ewing, Wilms, neuroblastomas, and ALL panels.

AZD6244 did not induce objective responses in any of the solid tumor panels or in the ALL panel. The best response to AZD6244 was PD2 (progressive disease with growth delay), with PD2 activity concentrated in the glioblastoma panel (2 of 4) and the osteosarcoma panel (3 of 6).

Constitutive phosphorylation of ERK was documented in the PPTP osteosarcoma xenografts (data not shown), indicating baseline MEK activation for the xenografts in this panel.

Potential areas of future focus in PPTP evaluations of AZD6244 include:

- Documenting the extent and duration of MEK inhibition at the doses/exposure evaluated for efficacy testing.
- Evaluating selected combinations of AZD6244 with other signal transduction inhibitors (e.g., rapamycin).