Abstract: LB-318  Pediatric Preclinical Testing Program (PPTP) Evaluation of the JAK Inhibitor AZD1480

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AZD1480 is a potent, competitive small molecule inhibitor of JAK1/2 kinase that has entered clinical evaluation.

The JAK/STAT pathway is active in a number of childhood cancers. JAK inhibition is of particular interest given the activating JAK1/2 mutations observed in a subset of pediatric acute lymphoblastic leukemia (ALL) cases.

AZD1480 was evaluated against the PPTP’s in vitro and in vivo panels.

The median relative IC50 (rIC50) for AZD1480 against the PPTP cell lines was 1.5 µM, with a range from 0.3 µM to 5.9 µM.

Neuroblastoma cell lines were relatively sensitive to AZD1480 (median rIC50 = 0.9 µM) with each cell line having a rIC50 value lower than the median for the entire panel.

AZD1480 activity

AZD1480 in vitro activity

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AZD1480 in vivo activity

 AZD1480 was provided for testing by AstraZeneca, and JAK-mutated ALL xenografts were developed in collaboration with the Children’s Oncology Group. Testing was supported by NCIC01462216.

AZD1480 inhibited significant differences in EFS distribution compared to control in 25 of 27 (93%) evaluable solid tumor models using a 60 mg/kg dose administered by oral gavage daily x 5 x 3 wks.

AZD1480 induced tumor growth inhibition with EFS T/C > 2 in 11 of 26 (42%) solid tumor xenografts.

AZD1480 induced a maintained CR in the KT-10 Wilms tumor xenograft. There was a sharp dose response curve for KT-10 with tumor regression activity lost at doses below 40 mg/kg/day.

For the ALL panel (using NOD-SCID mice), the MTD was lower, and a twice daily schedule was utilized: 10 mg/kg administered twice daily with a single daily dose of 15 mg/kg on weekends.

Only 1 of 9 (11%) of the evaluable ALL xenografts showed significant delay in time to event.

JAK mutated ALL xenografts were prioritized for testing to evaluate whether AZD1480 would show high activity in leukemia models in which the JAK-STAT pathway is activated by mutation. These models show phospho-STAT3 as evidence of JAK-STAT signaling. However, the only xenograft with EFS T/C > 2 was a JAK2 mutant (R867Q) model (TGT-020).

Phospho-STAT3 (pSTAT3) is present in many PPTP solid tumor xenografts. However, there is no relationship between pSTAT3 expression and response to AZD1480. For example, NB-1643 shows low expression of pSTAT3, but has EFS T/C > 2, while most of the osteosarcoma xenografts show marked pSTAT3 expression but have EFS T/C < 2. pSTAT3 is expressed by KT-10, but the expression is not prominent for KT-10 in comparison to other PPTP xenografts.

Whole genome sequencing is in process for the PPTP xenografts and may identify the genomic basis for the complete response of KT-10 to AZD1480.

Figure 1. AZD1480 activity in vivo against individual solid tumor xenografts using a dose of 60 mg/kg dose administered by oral gavage daily x 5 x 3 weeks. Kaplan-Meier curves for EFS (left), median relative tumor volume graphs (center), and individual tumor volume graphs (right) are shown for selected lines. Controls (gray lines); Treated (black lines).

Figure 2. AZD1480 activity in vivo against individual JAK2 mutated ALL xenografts at 10 mg/kg administered twice daily (with a single daily dose of 15 mg/kg on weekends). Kaplan-Meier curves for EFS (left), median relative tumor volume graphs (center), and individual tumor volume graphs (right) are shown for selected lines. Controls (gray lines); Treated (black lines).

Figure 3. Dose response to AZD1480 in KT-10 Wilms tumor xenografts tumor xenografts. Mice received AZD1480 at 20 mg/kg twice daily (XID) x 5 and 30 mg/kg SID at weekends (20-30) mg/kg BID and 10 mg/kg SID (weekends: 0-10) or 5 mg/kg BID and 7 mg/kg SID weekends: 5-7), or vehicle (Control) by oral gavage.

pSTAT3 EXPRESSION FOR PPTP XENOGRAFTS

IN VIVO RESULTS AND CONCLUSIONS

- AZD1480 induced significant differences in EFS distribution compared to control in 25 of 27 (93%) evaluable solid tumor models using a 60 mg/kg dose administered by oral gavage daily x 5 x 3 wks.
- AZD1480 induced tumor growth inhibition with EFS T/C > 2 in 11 of 26 (42%) solid tumor xenografts.
- AZD1480 induced a maintained CR in the KT-10 Wilms tumor xenograft. There was a sharp dose response curve for KT-10 with tumor regression activity lost at doses below 40 mg/kg/day.
- For the ALL panel (using NOD-SCID mice), the MTD was lower, and a twice daily schedule was utilized: 10 mg/kg administered twice daily with a single daily dose of 15 mg/kg on weekends.
- Only 1 of 9 (11%) of the evaluable ALL xenografts showed significant delay in time to event.
- JAK mutated ALL xenografts were prioritized for testing to evaluate whether AZD1480 would show high activity in leukemia models in which the JAK-STAT pathway is activated by mutation. These models show phospho-STAT3 as evidence of JAK-STAT signaling. However, the only xenograft with EFS T/C > 2 was a JAK2 mutant (R867Q) model (TGT-020).
- Phospho-STAT3 (pSTAT3) is present in many PPTP solid tumor xenografts. However, there is no relationship between pSTAT3 expression and response to AZD1480. For example, NB-1643 shows low expression of pSTAT3, but has EFS T/C > 2, while most of the osteosarcoma xenografts show marked pSTAT3 expression but have EFS T/C < 2. pSTAT3 is expressed by KT-10, but the expression is not prominent for KT-10 in comparison to other PPTP xenografts.
- Whole genome sequencing is in process for the PPTP xenografts and may identify the genomic basis for the complete response of KT-10 to AZD1480.