Pediatric Preclinical Testing Consortium Evaluation of AZD1775 as a Single Agent and in Combination with Irinotecan

Introduction

HEWI1 behaves a central role in the G2-M cell cycle checkpoint and is also required during S-phase. ATP12 is required for progression from G2 to M phase. HEWI1 maintains CDK1 in an inactive state through phosphorylation at threonine 15. HEWI1 is activated in response to single-stranded DNA breaks in series of steps beginning with ATM activation leading to CHK1 phosphorylation, with CHK1 then phosphorylating and activating WEHI1 leading to CDK1 phosphorylation and inactivation. In an inactive state through phosphorylation at threonine 15.

Study Methods

For comparing treatment groups, comparison between treatment groups used a p-value of 0.0167 for agents. More than 30 clinical trials are evaluating AZD1775 with DNA-damaging agents. Preclinical studies have shown the ability of AZD1775 to potentiate a range of cytotoxic agents, including topoisomerase-I inhibitors, antimetabolites, and DNA cross-linking agents.

AZD1775 is a potent and selective ATP-competitive inhibitor of WEHI1. The EFS was significantly longer for the combination compared to single agent irinotecan in all models tested. The magnitude of the increase in EFS was greater for the osteosarcoma and Wilms tumor xenografts than for the neuroblastoma xenografts. The combination study also induced significantly lower minimum relative tumor volumes (mRTVs) for all xenograft lines studied when compared to the mRTVs induced by single agent irinotecan.

Results

3. Results: Response to AZD1775, Irinotecan and the Combination

The following treatment groups were used to evaluate the activity of single agent AZD1775 to determine if adding AZD1775 to irinotecan was more effective than either of the single agents.

- CR = complete response, disappearance of measurable tumor mass during study period (For ALL: %huCD45+ never drops below 1% and reaches event before the end of the study, with an EFS > 200% of median control EFS)

- PD1 = when PD and the mouse’s time to event ≤ 200% the KM median time-to-event

- PD2 = when PD but, additionally, time-to-event is > 200% of the Kaplan-Meier (KM) median time-to-event (see Table).

The objective response measure improved for 1 neuroblastoma (NB-1643: PR to CR), 2 osteosarcomas (OS-1 and OS-33: PD1 to PD2), and 1 Wilms tumor (KT-13: PD2 to PR) xenograft lines.

Additional sarcoma and Wilms tumor lines are currently being tested to further understand the range of potentiation of irinotecan by AZD1775 for pediatric solid tumors. When considered with recently reported AZD1775 combination testing results for other chemotherapy, these results support pediatric clinical evaluations of AZD1775 in combination with irinotecan, as is ongoing in NCT02095132.

4. Discussion and Conclusions

AZD1775 showed no single agent activity against the pediatric solid tumor xenografts studied, but it potentiated the activity of irinotecan to some extent for all of the xenografts studied.

References


More Information