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

1. Introduction

AZD1775 was supplied to the PPTC by AstraZeneca.

2. Study Methods

3. Results

4. Discussion and Conclusions

5. References

Pediatric Preclinical Testing Consortium

A program funded by the National Cancer Institute and the National Institutes of Health


1Greehey Children’s Cancer Research Institute, San Antonio, TX; 2MD Anderson, Houston, TX; 3Nemours Center for Cancer and Blood Disorders, Wilmington, DE; 4Children’s Hospital of Philadelphia, Philadelphia, PA; 5RTI International, Research Triangle Park, NC; 6National Cancer Inst., Bethesda, MD

1. Introduction

The PPTC sought to evaluate the ability of AZD1775 to potentiate the in vivo activity of antitumor agents, including topoisomerase-I inhibitors, antimetabolites, and DNA cross-linking agents.

3. Results

AZD1775 in Vivo Single-Agent and Combination Activity with Irinotecan

The objective response categories are as described by Houghton, et al. 2007.

The objective response measure improved for 1 neuroblastoma line (NB-1643: PR to PD2), and 1 Wilms tumor line (KT13: PD2 to PR) in the combination of AZD1775 + irinotecan induced objective responses in two neuroblastoma lines (PRs for NB-1643 and NB-Ebc1), and the combination of AZD1775 + irinotecan induced objective responses in the same two neuroblastoma lines (PR and CR) as well as a PR in KT13 and a Wilms tumor line.

The EFS range was greatest for the osteosarcoma and Wilms tumor xenografts rather than for the neuroblastoma xenografts. The combination also induced significantly smaller median relative tumor volumes (mrTIVs) for all xenograft lines studied when compared to the single-agent treatments.

5. References

Among the lines tested, the osteosarcoma lines lack TP53 activity through absent TP53 expression, while KT-13 and NB-SD have mutant TP53 (p.C174Y and p.C179F, respectively), the wild-type expression of chemopotentiation among the combination treatments was tested for greater with defective TP53.

Additional sarcoma and Wilms tumor lines are currently being further utilized to understand the range of potentiation of irinotecan by AZD1775 in pediatric solid tumors.

When considered with recently reported ADZ1775 combination testing results for Habakuk313756 (Stewart, et al. 2017), these results support further preclinical evaluations of AZD1775 in combination with irinotecan, as is ongoing.

4. Discussion and Conclusions

Irinotecan induced objective responses in two neuroblastoma lines (PRs for NB-1643 and NB-Ebc1), and the combination of AZD1775 + irinotecan induced objective responses in the same two neuroblastoma lines (PR and CR) as well as a PR in KT13 and a Wilms tumor line.

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.

Irinotecan potentiated the effects of irinotecan across all of the xenograft lines tested, the magnitude of potentiation of irinotecan by AZD1775 appeared greater for the neuroblastoma and Wilms xenografts compared to the osteosarcoma lines.

The relationship between TP53 status and chemopotentiation by AZD1775 is controversial.


The range of potentiation of irinotecan by AZD1775 for pediatric solid tumors.