Pediatric Preclinical Testing Consortium (PPTC) Evaluation of the EZH2 Inhibitor Tazemetostat in Orthotopic PDX Models of Pediatric Brain Tumors

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1. Introduction

RAG-2 SCID and NOD SCID mice, 6-8 week old, both genders

Cell suspension: 1x10^5 cells (2 µL for IC and ICb)

– Depth: 3 mm from cranial surface

2. Study Methods (continued)

Objective

To determine the in vivo therapeutic efficacy of tazemetostat in pediatric brain tumor models with over-expressed EZH2

Drug Treatment and Study Design

➢ Timing: Drug treatment started 2 weeks after tumor implantation (day 14)

➢ Sample size: 10 mice per treatment group in each PDX model

➢ Endpoint: Mice euthanized once severe neurologic deficits developed or became thin, slow moving, and hunched

➢ Analysis: Differences in event-free survival (EFS) between treatment groups were tested using an exact log-rank test

3. Results

3.1 Results (continued)

ICb-1078MB

Group 4

- EZH2 mRNA ~ 6 folds
- H3K27me3 amplification
- MLC amplification and over-expression

Group 3

- EZH2 mRNA ~ 3 folds
- H3K27me3 amplification

Group 2

- EZH2 mRNA ~ 2 folds
- H3K27me3 amplification

Group 1

- Control

ICb-3752MB

Group 3

- EZH2 mRNA ~ 3 folds
- GARD44 increase mutation

Group 2

- EZH2 mRNA ~ 2 folds
- GARD44 increase mutation

Group 1

- Control

4. Discussion and Conclusions

➢ Inhibition of EZH2 with tazemetostat given as a single agent or in combination with cisplatin, radiation, or both was not effective at prolonging the survival of group 3 or 4 multilobar PDX models.

➢ Inhibition of EZH2 with high-dose tazemetostat (400 mg/kg) given as a single agent prolonged the survival of a SEB subgroup ATRT PDX model

➢ Inhibition of EZH2 with tazemetostat given as a single agent prolonged the survival of a pediatric GBM PDX model compared to control, but tazemetostat addition in radiation therapy did not prolong survival beyond that observed with radiation alone.

5. References


More Information

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Translational Studies of the NCI’s PPTC. www.nci.gov/pptc