Inhibition of mutant IDH enzymes reduces production of 2-HG but does not restore wild-type IDH activity in vitro or in vivo

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OBJECTIVES

- To determine whether inhibition of wtIDH in cells could be correlated with the activity observed in vivo
- To determine whether the IC50 of IVO and VOR are suitable for use in clinical trials

METHODS

- In vivo plasma exposures to determine IC50 of IVO and VOR in HCT-116+/+ tumors
- To determine the in vivo inhibition of wtIDH activity in HCT-116+/+ tumors
- To determine the in vivo inhibition of wtIDH activity in HCT-116+/R132H tumors
- To determine the in vivo inhibition of wtIDH activity in HCT-116+/mIDH1 tumors

RESULTS

- VOR and IVO in vitro inhibited wtIDH activity, with IC50 values of 0.32 (0.2) µM and 0.006 (0.8) µM, respectively.
- The in vivo inhibition of wtIDH activity in HCT-116+/+ tumors was 95%, 94%, and 92% at 0.5, 5, and 50 mg/kg QD VOR, respectively. 0.5, 5, and 50 mg/kg QD VOR reduced 2-HG by 82%, 94%, and 95%, respectively.
- The in vivo inhibition of wtIDH activity in HCT-116+/R132H tumors was 52%, 54%, and 55% at 0.5, 5, and 50 mg/kg QD VOR, respectively. 0.5, 5, and 50 mg/kg QD VOR reduced 2-HG by 76%, 88%, and 92%, respectively.
- The in vivo inhibition of wtIDH activity in HCT-116+/mIDH1 tumors was 38%, 40%, and 42% at 0.5, 5, and 50 mg/kg QD VOR, respectively. 0.5, 5, and 50 mg/kg QD VOR reduced 2-HG by 59%, 71%, and 73%, respectively.

CONCLUSIONS

- The in vivo inhibition of wtIDH activity in HCT-116+/+ tumors was 95%, 94%, and 92% at 0.5, 5, and 50 mg/kg QD VOR, respectively, and 2-HG levels were reduced by 82%, 94%, and 95%, respectively.
- The in vivo inhibition of wtIDH activity in HCT-116+/R132H tumors was 52%, 54%, and 55% at 0.5, 5, and 50 mg/kg QD VOR, respectively, and 2-HG levels were reduced by 76%, 88%, and 92%, respectively.
- The in vivo inhibition of wtIDH activity in HCT-116+/mIDH1 tumors was 38%, 40%, and 42% at 0.5, 5, and 50 mg/kg QD VOR, respectively, and 2-HG levels were reduced by 59%, 71%, and 73%, respectively.