Two novel DNMT1 inhibitors: 4'-Thio-2'-Deoxycytidine (TdCyd) and 5'-aza-4'-Thio-2'-Deoxycytidine (aza-TdCyd) for the treatment of MEN1 tumors in a preclinical study

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Introduction
We have demonstrated that inactivation of menin (the protein product of MEN1) increases activity of DNMT1 and mediates DNA hypermethylation in the development of multiple endocrine neoplasia type 1 (MEN1) syndrome1-2. Our collaborators at the NCI developed two novel DNMT1 inhibitors: TdCyd and aza-TdCyd, both of which inhibit aberrant DNMT1 activity in tumor cells.

In the present study, we explored the anti-neoplastic activity and the molecular mechanism of these novel DNMT1 inhibitors in the inhibition of DNMT1 enzyme activity, reduction of tumor proliferation, and induction of apoptosis by using our novel NET mouse models.

Materials and Methods
DNMT1 inhibitors: Two novel DNMT1 inhibitors: 4'-Thio-2'-Deoxycytidine (TdCyd) and 5'-aza-4'-Thio-2'-Deoxycytidine (aza-TdCyd) were obtained from our collaborators at the National Cancer Institute (NCI).

Men1 KO mice: We developed a Men1 conditional KO mouse model that develops islet hyperplasia at 6 months and insulinomas at 12 months.

DNMT1 inhibitors to treat MEN1 tumors: 15 Men1 KO mice at 12 months of age with insulinomas and hyperinsulinemia were divided into three groups and were ip injected with TdCyd (2mg/kg), aza-TdCyd (1 mg/kg), or PBS (100 µl) as a control, respectively.

DNMT1 inhibitors to prevent MEN1 tumorigenesis: 15 younger Men1 KO mice at 3 months of age were divided into three groups and ip injected with TdCyd, aza-TdCyd, or PBS control, respectively.

The agents were given in 21-day cycles. The agents were administered to the mice once a day during week 1 for 5 days. Agents were then administered for 5 days during week 2. No agents were administered during week 3.

Conclusions
Our studies indicate that both DNMT1 inhibitors, TdCyd and aza-TdCyd, are safe and effective for the treatment of MEN1 related pancreatic tumors in the pre-clinical setting. Since these agents have been safely administered to patients in phase 1 trials, we believe that our study supports the development of DNMT1 inhibitors as a treatment for patients with MEN1 associated tumors.

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References