A phase 1 trial of AG-270 in patients with advanced solid tumors or lymphoma with homozygous MTAP deletion

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BACKGROUND
- Homozygous deletion of MTAP (e.g. homozygous diethylaminoethyltransferase, methylnitrosourea, methylthioadenosine, methylthiouracil, methylthioadenosine) is found in ~7% of human tumors.
- MTAP deletion frequency correlates with the presence of chronic lymphocytic leukemia, which is a well-documented prognostic factor in cancer.
- Deregulation of MTAP results in the accumulation of the enzyme’s substrates, methylthioadenosine (MTA), and methylthioadenosine (MTA).
- Increased concentrations of MTA partially inhibit the activity of poly ADP-ribose polymerase (PARP), thus multiple mechanisms are thought to be involved in PARP inhibition.
- Inhibition of PARPs acetylates activity in reduction of symptoms/methylation in patients with MTAP deletion. Therapy, some of which are associated with MTA accumulation, is a potential treatment option for patients with MTAP deletion.

OBJECTIVE AND METHODS
- To report preliminary results from the ongoing, first-in-human, phase 1 trial of AG-270 in patients with homozygous deletion of MTAP (Figure 2). (Table 1)

RESULTS
- As of Aug 14, 2018, 27 patients had been treated (Available online). (Table 1)
- A 53-year-old patient with a refractory, progressive sex cord stromal tumor continues to have stable disease after 12.8 months of AG-270 at 50 mg QD shown (Figure 4). (Table 7)
- Of the 27 patients, 11 (41%) had a confirmed partial response and 1 (3%) had a complete response. (Table 1)
- A 53-year-old patient with a refractory pancreatic cancer continues to have stable disease after 12.8 months of AG-270 at 50 mg QD shown (Figure 4).

CONCLUSIONS
- AG-270 is the first MAT2A inhibitor to be evaluated in humans. (Figure 6)
- AG-270 demonstrates clinical activity in patients with tumors that are methylthioadenosine-null and/or CDKN2A-null.
- AG-270 is currently being evaluated in a phase 1b study in patients with ARID1A null cancers starting with an AG-270 dose of 100 mg QD (Figure 2).

Table 1. Enrollment and demographics
- N=39
- TRIAL: NCT03435250

Table 2. Summary of AEs and dose-limiting toxicities by dose cohort
- N=20
- AG-270 was generally well tolerated. (Table 2)
- AG-270 was generally well tolerated. (Table 2)

Table 3. Summary of AEs and dose-limiting toxicities by dose cohort
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Table 4. Reductions in plasma SAM concentration at steady state (C1D15)
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Table 7. Summary of AEs and dose-limiting toxicities by dose cohort
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Table 9. Summary of AEs and dose-limiting toxicities by dose cohort
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Table 10. Summary of AEs and dose-limiting toxicities by dose cohort
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Table 11. Summary of AEs and dose-limiting toxicities by dose cohort
- N=20
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Table 12. Summary of AEs and dose-limiting toxicities by dose cohort
- N=20
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Table 13. Summary of AEs and dose-limiting toxicities by dose cohort
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Table 14. Summary of AEs and dose-limiting toxicities by dose cohort
- N=20
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Table 15. Summary of AEs and dose-limiting toxicities by dose cohort
- N=20
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Table 16. Summary of AEs and dose-limiting toxicities by dose cohort
- N=20
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Table 17. Summary of AEs and dose-limiting toxicities by dose cohort
- N=20
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Table 18. Summary of AEs and dose-limiting toxicities by dose cohort
- N=20
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Table 19. Summary of AEs and dose-limiting toxicities by dose cohort
- N=20
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Table 20. Summary of AEs and dose-limiting toxicities by dose cohort
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