The MAT2A inhibitor AG-270 combines with both taxanes and gemcitabine to yield enhanced antitumor activity in patient-derived xenograft models

Marc L Hyer, Peter Kalev, Mark Fletcher, Chi-Chao Chen, Elia Aguado-Fraile, Everton Mandley, Sheila Newhouse, Max Lein, Raj Nagaraja, Yisem Tuncay, Josh Murtele, Scott A Biller, Kevin M Marks, Katya Marjon

Agios Pharmaceuticals, Inc., Cambridge, MA, USA
Marc.Hyer@agios.com

The MAT2A inhibitor AG-270 disrupted splicing and altered gene expression in vivo.

**BACKGROUND**

- AG-270 is a first-in-class, orally-available inhibitor of methyltransferase-like 1 (METTL1) currently being evaluated in a phase I trial in patients with advanced solid tumors and lymphoma with METTL1 (or METTL1-like) defects.

**RESULTS**

- A large-scale syngeneic screen created potential syngeneic combinations (Figure 2).

**OBJECTIVES**

- To identify combinatorial partners for AG-270, as a single agent in vivo using a syngeneic mouse model.

**METHODS**

- A 41-taxane screen tested 21 combinatorial candidates in 27 syngeneic cell lines, with survival curve responses performed at necropsy using the Caliper Cell-Titer96 assay.

**CONCLUSIONS**

- A cell-based screen identified taxanes and gemcitabine as therapeutic agents that could potentiate combination benefit with AG-270.

**REFERENCES**

Some of these data were previously presented in Kalev P et al. 2018;2:401–4.
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These preclinical findings have inspired an ongoing phase 1 study exploring AG-270 combined with docetaxel: dosing of the first patient has been completed.

**Figure 1.** Targeting MAT2A in cancer with AG270. MAT2A inhibitor--induced chromosomal split/aneuploidies in NCI-HCT116 control and MTAP--/-- xenograft tumors.

**Figure 2.** AG-270 synergizes with autotaxin and gemcitabine in a cell-based assay.

**Figure 3A.** MAT2A inhibitor--induced detained introns included genes involved in the DNA damage response.

**Figure 3B.** Donor intron--containing transcripts fail to export into the cytosol and thus are not translated.

**Figure 4.** AG-270 enhanced docetaxel in an NSCLC (SCC) MTAP--/-- PDX model.

**Figure 5.** AG-270 enhanced docetaxel in an NSCLC (SCC) MTAP--/-- PDX model.

**Figure 6.** AG-270 enhanced docetaxel in an NSCLC (SCC) MTAP--/-- PDX model.

**Table 1.** Efficacy data summary of AG-270 and gemcitabine, alone and combined.

**Table 2.** Efficacy data summary of AG-270 and gemcitabine, alone and combined.

**Figure 7.** AG-270 enhanced docetaxel therapy in an NSCLC (SCC) PDX mouse model.

**Table 3.** Efficacy data summary of AG-270 and gemcitabine, alone and combined.

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