5-Azacytidine inhaled dry powder formulation profoundly improves pharmacokinetics and efficacy for lung cancer therapy through genome reprogramming

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BACKGROUND: Epigenetic therapy through demethylation of 5-methylcytosine has been largely ineffective in treating lung cancer, most likely due to poor tissue distribution with oral or subcutaneous delivery of drugs such as 5-azacytidine (5AZA). An inhalable, stable dry powder formulation of 5AZA was developed.

METHODS: Pharmacokinetics of inhaled spray-dried dry powder and aqueous formulations of 5AZA were compared to an injected formulation. Efficacy studies and effect of therapy on the epigenome were conducted in an orthotopic rat lung cancer model for inhaled formulations.

RESULTS: Inhaled dry powder 5AZA showed superior pharmacokinetic properties in lung, liver, brain and blood compared to the

injected formulation and for all tissues except lung compared to an inhaled aqueous formulation. Only dry powder 5AZA was

detected in brain (~4-h half-life). Inhaled dry powder was superior to inhaled aqueous 5AZA in reducing tumor burden 70–95%.

Superiority of inhaled 5AZA dry powder was linked to effectively reprogramming the cancer genome through demethylation and gene expression changes in cancer signaling and immune pathways.

CONCLUSIONS: These findings could lead to widespread use of this drug as the first inhaled dry powder therapeutic for treating local and metastatic lung cancer, for adjuvant therapy, and in combination with immunotherapy to improve patient survival.