ND-646 Leads to Potent Inhibition of Breast Cancer Cell Growth in vitro and in vivo

Modulation of Lipid Metabolism Through Inhibition of Acetyl-CoA Carboxylase with ND-646

Jennifer L. Rocnik1, Wenyen Miao2, Geraldine Harriman1, Jeremy Greenwood2, Sathish Bhat3, H. James Harwood1, Rosana Kapeller1, William F. Westlin1

ND-646 is a potent allosteric inhibitor of ACC1/2 with good drug-like properties.

Treatment of human breast cancer cell lines with ND-646 resulted in inhibition of proliferation of selected cell lines in vitro.

ND-646 was well tolerated and significantly inhibited growth of MD-A-MB-468 orthotopic tumors.

ND-646 demonstrated prolonged target engagement in tumor tissue and induction of apoptosis in MDA-MB-468 tumors.

Profiling of ND-646 is ongoing to identify predictors of response and identify novel clinical endpoints.

**ABSTRACT**

Metabolic attenuation is a promising approach to cancer therapy and rate-limiting steps in key biosynthetic pathways are particularly attractive targets. Many cancer types are dependent on fatty acid synthesis as a primary source of energy and for providing lipids for expansion of cell and nuclear membranes in rapidly proliferating cells. The rate-limiting enzyme in fatty acid synthesis, acetyl-CoA carboxylase (ACC), has been shown to be highly expressed in human breast cancer. ACC is thought to be critical for the growth and survival of cancer cells, especially within a tumor microenvironment where exogenous fatty acids might be limited. Effective therapeutic options for triple negative breast cancer are limited and identification of robust targeted agents without overt toxicity for this indication are especially needed. Dual inhibition of the ACC isoforms, ACC1 and ACC2, results in concomitant inhibition of fatty acid synthesis and stimulation of fatty acid oxidation. We have identified ND-646, a potent, selective, allosteric inhibitor of ACC1 and ACC2, results in concomitant inhibition of fatty acid synthesis and stimulation of fatty acid oxidation.

**Growth and Survival of Cancer Cells**

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**CONCLUSIONS**

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