FAK Inhibitor VS-4718 Preferentially Attenuates Growth of Malignant Mesotheliomas with NF2 Mutation: Role of Cancer Stem Cells

Irina M. Shapiro1, Vihren N. Kolev1, Christian M. Vidal1, Mitchell Keegan1, Qunli Xu1, Craig Menges2, Joseph R. Testa2 and Jonathan A. Pachter1
1Verastem, Inc., Cambridge, MA and 2Fox Chase Cancer Center, Philadelphia, PA

ABSTRACT
Malignant pleural mesothelioma (MPM) is an aggressive tumor in the pleural lining of the lung often caused by asbestos exposure. MPM patients are usually diagnosed at an advanced stage of the disease and the prognosis is poor. Median survival after diagnosis is 9 to 12 months and standard-of-care agents such as cisplatin and pemetrexed are relatively ineffective in increasing median survival time for MPM patients. New therapeutic modalities are urgently needed to improve the prognosis of MPM patients.

Neurofibromatosis 2 (NF2) is a tumor suppressor gene that encodes the protein Merlin. Biallelic inactivation of NF2 by mutation and/or deletion occurs in ~40% of MPMs leading to inactive Merlin. Merlin has been demonstrated to play roles in cell adhesion, invasion and cell motility in tumor cell lines partially through regulation of focal adhesion kinase (FAK) which in turn mediates signal transduction by integrins and growth factor receptors. Increased activation of FAK has been demonstrated in NF2-mutated mesothelioma cells, indicating that FAK may represent an important therapeutic target for MPM.

VS-4718, a selective FAK kinase inhibitor was evaluated in a panel of MPM cell lines with wild-type or mutated NF2. Mutant NF2 MPM cell lines were found to be especially sensitive to the FAK inhibitor VS-4718 with EC50 values below 100 nM, in contrast to wild type NF2 MPM cell lines which were less sensitive to pemetrexed, but sensitive to VS-4718 for treatment of NF2 mutant mesothelioma. We believe that these data support the clinical response. Furthermore, cancer stem cells in NF2 mutant mesothelioma appear to be particularly resistant to pemetrexed, but sensitive to VS-4718. These data provide rationale for clinical trials of a FAK inhibitor in patients with malignant mesothelioma.

INTRODUCTION
ECM

ECM

MERLIN

FAK

NF2

Problem:

Initial Tumor

Current cancer treatments

Recurrent Tumor

CSC drugs + current cancer treatments

Durable clinical response

Goal:

Initial Tumor

CSC drugs + current cancer treatments

Tumor reduction and ablation

Tumor reduction and ablation of CSCs

METHODS
Aldehyde dehydrogenase (ALDH) – cancer stem cell marker:
• A detoxifying enzyme
• Oxidizes intracellular aldehydes
• Plays a role in stem cell differentiation through metabolism of retinal to retinoic acid
• Activity is assessed by the fluorescent Aldefluor assay

CONCLUSIONS
• The selective FAK inhibitor VS-4718 shows increased potency in mesothelioma cell lines lacking NF2/Merlin.
• Mesothelioma cancer stem cells (CSCs) are stimulated by standard-of-care agents, but ameliorated by VS-4718.
• VS-4718 significantly inhibits growth of Merlin-negative mesothelioma tumors in a mouse orthotopic model.
• NF2/Merlin status may be a valuable stratification marker for FAK inhibitor response.
• These data provide rationale for clinical trials of a FAK inhibitor in patients with malignant mesothelioma.