The cancer stem cell inhibitors VS-6063 (defactinib) and VS-5584 exhibit synergistic anticancer activity in preclinical models of mesothelioma

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ABSTRACT
Malignant pleural mesothelioma is an aggressive cancer of the lining of the lung in which cancer stem cells may drive resistance to current chemotherapy. There is only one treatment regimen approved for use, pemetrexed plus a platinum agent, which is used as front-line therapy and results in median overall survival of only 12 months. Unfortunately, there are no approved second line options for patients with actively progressing disease after front-line therapy.

RESULTS
Fig 2: Screening for drugs exhibiting synergistic anticancer activity with VS-6063.

An in vitro combination screen was carried out to identify anticancer drugs that exhibit synergistic anticancer activity with VS-6063. Multiple cell lines were treated with VS-6063 and 20 anticancer agents in matrigel with a full 10x10 matrix format. Combination activity was assessed using Highest Single Agent (HSA), Loewe additivity and Bliss models.

INTRODUCTION
Fig 1: Critical to target cancer stem cells for a durable clinical response

Problem: Malignant pleural mesothelioma

Solution: 
- VS-6063 and VS-5584 selectively target CSCs
- PI3K/mTOR inhibition may combine for more robust shut down of AKT survival signaling

SUMMARY
- VS-6063 (defactinib) is a potent/selective FAK kinase inhibitor.
- VS-5584 is a potent/selective inhibitor of PI3K & mTORC1/2.
- Both agents preferentially target CSCs in preclinical mesothelioma models.
- Synergistic activity of VS-6063 & VS-5584 on CSCs & bulk tumor has been observed in preclinical models.
- These data provide preclinical rationale for a planned Phase I combination study of VS-6063 & VS-5584 in patients with relapsed mesothelioma.