

POSTER PRESENTATION

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Discovery of a PFKFB3 inhibitor for phase I trial testing that synergizes with the B-Raf inhibitor vemurafenib

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Background

In human cancers, loss of PTEN, stabilization of hypoxia inducible factor-1 α , and activation of Ras and AKT converge to increase the activity of a regulator of glycolysis, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB3). This enzyme synthesizes fructose-2,6-bisphosphate (F2,6BP), which is an activator of 6-phosphofructo-1-kinase, a key step of glycolysis that is tightly controlled by multiple metabolic feedback mechanisms. We recently identified the first competitive small molecule inhibitor of PFKFB3, 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3PO), and have now sought to develop a more potent PFKFB3 inhibitor with improved PK properties for testing in clinical trials.

Materials and methods

Methods included recombinant PFKFB3 assays, PK studies using mass spectrometry, pre-clinical toxicity and efficacy studies, Western blot analyses for HIF-1 α and PFKFB3 in A375 melanoma cells, F2,6BP assessments and flow cytometry for apoptosis.

Results

We report the discovery of a novel 3PO-derivative, PFK158, that is more potent than 3PO, has improved PK properties and causes ~80% growth inhibition in several mouse models of human-derived tumors. We also demonstrate that PFK158 is well tolerated in rats and dogs providing key support for a phase 1 trial in cancer patients that will initiate in 2014. Once the MTD is established, we intend to conduct multiple phase 1/2 trials of PFK158 in

combination with targeted agents given the ability of PFK158 to suppress glycolysis. 50% of melanomas harbor a BRAF^{V600E} mutation that promotes glucose metabolism, survival and proliferation and BRAF^{V600E} inhibitors are effective in ~50% of melanoma patients. Unfortunately, resistance to these agents develops within six months and most patients die within two years of diagnosis. Genetic amplifications of BRAF^{V600E} are a common cause of resistance, and BRAF^{V600E} stabilizes HIF-1 α , an established promoter of PFKFB3. We thus hypothesized that PFKFB3 may be essential for intrinsic resistance to BRAF^{V600E} inhibitors. In unpublished results, we demonstrate that 3 hours of exposure to 1 μ M vemurafenib reduces HIF-1 α , PFKFB3, and F2,6BP in BRAF^{V600E} positive A375 melanoma cells and that PFK158 markedly sensitizes these cells to the apoptotic effects of vemurafenib.

Conclusions

In conclusion, PFK158 is the first PFKFB3 inhibitor to be examined in a phase I trial and may have significant clinical utility when combined with agents that target driver oncogenes. Importantly, our data provide rationale for the conduct of pre-clinical studies of PFK158 combined with vemurafenib in transgenic BRAF^{V600E} melanoma mouse models which are in turn expected to justify a phase 1/2 trial of the combination in BRAF^{V600E}-positive melanoma patients.

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