FAK/PYK2 INHIBITION ENHANCES IMMUNE CHECKPOINT INHIBITOR EFFICACY

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ABSTRACT

Although durable responses to single agent immune checkpoint inhibitors have been reported, additional approaches are needed to extend this therapeutic benefit to a greater proportion of patients. Combination of immunotherapy agents with tumor microenvironment modulators has the potential to overcome barriers that tumor cells develop to evade the immune system, and provide benefit to a greater proportion of patients. Focal Adhesion Kinase (FAK) and the family member PYK2 are potentially valuable targets due to their roles in regulating key cellular populations in the tumor microenvironment. In addition to targeting cancer stem cells, the FAK/PYK2 dual inhibitors, VS-6063 and VS-4718, have been shown to inhibit monocytic-derived macrophages, reduce tumor-associated macrophages in xenograft models, and promote a CD8+ T cell-mediated anti-tumor response in squamous cell carcinoma models.

We now report the combination of VS-4718 with an anti-PD-1 mAb shows improved efficacy over anti-PD-1 mAb alone and extends survival of MC38 syngeneic tumor bearing animals. Analysis of MC38 tumors at day 12 of treatment revealed a significant increase in the CD8+ T cell/Treg ratio in tumors in the VS-4718 + anti-PD-1 combination group, providing a mechanistic understanding for the enhanced efficacy of this combination.

To explore additional combination options, we tested the combination of VS-4718 with anti-4-1BB in the MC38 model. Consistent with what was observed with the anti-PD-1 combination, VS-4718 also enhances the efficacy of an anti-4-1BB mAb.

To further delineate the effect of FAK inhibition, an in vitro T cell proliferation assay was conducted. VS-6063 and VS-4718 dose-dependently stimulated proliferation of CD8+ cytotoxic T cells isolated from healthy donors. This is in distinct contrast to other protein kinase inhibitors, such as the SRC inhibitor dasatinib which potently impaired the proliferation of CD8+ cytotoxic T cells. In addition, both VS-4718 and VS-6063 decreased CD8+ T cell exhaustion markers, and increased T cell-mediated tumor cell killing in vitro.

These data provide a rationale for clinical trials in cancer patients to test whether a FAK/PYK2 inhibitor in combination with an immune checkpoint inhibitor could increase the breadth of responsive tumor types, increase the number of responders, and confer more durable anti-tumor response.

RESULTS

Combination of VS-4718 + anti-PD1 improves anti-tumor efficacy in syngeneic MC38 colorectal tumor-bearing mice

Data are presented as fold-change vs. DMSO control wells.

P < 0.03

Decreased Tregs and increased CD8+ T cells with VS-4718 + anti-PD1 combination in MC38 Tumors

Combination of VS-4718 + anti-4-1BB improves anti-tumor efficacy in syngeneic MC38 colorectal tumor-bearing mice

Figure 1: Effects of FAK/PYK2 inhibitor on tumor microenvironment

Figure 2: Syngeneic MC38 tumors were randomized once tumors reached 50-100mm³ and then treated with either vehicle, VS-4718 (75 mg/kg, BID, po through end of experiment), anti-PD1 (clone RMP1-14, 10 mg/kg i.p. on days 1, 4, 8, 11) or VS-4718 + anti-PD1.

Figure 3: Syngeneic MC38 tumors were randomized once tumors reached 50-100mm³ and then treated with either vehicle, VS-4718 (75 mg/kg, BID, po), anti-4-1BB (clone LOB12.3, 10 mg/kg i.p. on days 1, 4, 8, 11) or VS-4718 + anti-4-1BB.

Figure 4: Syngeneic MC38 tumors were randomized once tumors reached 50-100mm³ and then treated with either vehicle, VS-4718 (75 mg/kg, BID, po), anti-LAG3 (clone 1H11, 10 mg/kg i.p. on days 1, 4, 8, 11) or VS-4718 + anti-LAG3.

Figure 5: Antigen-specific CD8+ T cells were co-cultured with cognate IP-10+ tumor cells at various E:T ratios in the presence of VS-6063 on top of Matrigel. After 24 hours, cultures were analyzed for changes in IFN-Î³ release as a measure of tumor cell viability.

Figure 6: CD8+ T cells were isolated from fresh, healthy human PBMCs by negative immunomagnetic bead separation. Purified CD8+ T cells were plated on CD3-coated plates in the presence or absence of VS-4718 or VS-6063 for 72 hours. Assay wells were pulsed with BrdU for the last 3-4 hours of culture and subjected to a BrdU-incorporation assay for the determination of actively proliferating cells. Data are presented as fold-change vs. DMSO control wells.

Figure 7: CD8+ T cells isolated from fresh, healthy human PBMCs by negative immunomagnetic bead separation were plated on anti-CD3 coated plates in the presence of VS-4718 or VS-6063 for 72 hours and then harvested and stained with anti-LAG3 or anti-PD-1 for flow cytometric analysis.

SUMMARY

• FAK inhibitors change the tumor immune balance to potentiate efficacy of various immunotherapy agents
  - FAK inhibitor combination substantially enhances anti-tumor efficacy of anti-PD-1 or anti-LAG3 vs. each immuno-oncology antibody alone
  - FAK inhibitor + anti-PD-1 combination decreases Tregs and increases CD8+ T cells in MC38 tumors
  - FAK inhibitors increase CD8+ T cell proliferation, decrease CD8+ T cell exhaustion markers, and increase T cell-mediated tumor cell killing in vivo
  - These data provide rationale for clinical use of a FAK inhibitor in combination with immuno-oncology antibodies

  - Supports the ongoing VS-6063 combination trial with pembrolizumab (anti-PD-1) and gemcitabine in pancreatic cancer (NCIT025463531) & the clinical testing of VS-6063 + avelumab (anti-PD-L1) in ovarian cancer

DeCREASES INCREASES

Cytotoxic (CD8+) T cells
Immune-Suppressive Cells
MDSCs, Tregs, M2 tumor-associated macrophages

More favorable tumor microenvironment for enhanced efficacy of Immuno-Oncology therapeutics

In vitro