Wnt pathway antagonist OMP-54F28 (FZD8-Fc) inhibits tumor growth and reduces tumor-initiating cell frequency in patient-derived hepatocellular carcinoma and ovarian cancer xenograft models.

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ABSTRACT

The Wnt/beta-catenin pathway, which signals through the Frizzled (FZD) receptor family and several co-receptors, has been long implicated in cancer. We have developed OMP-54F28, a recombinant fusion protein consisting of the extracellular ligand-binding domain of FZD8 and a human IgG1 Fc fragment. OMP-54F28 acts as a decoy receptor in sequestering Wnt and preventing them from binding to FZD receptors and thereby inhibiting Wnt signaling. The Wnt pathway is important for stem cell self-renewal, differentiation, tumorigenesis, and epithelial-mesenchymal transition (EMT). Using minimally passaged human patient-derived xenograft tumors, we demonstrate that OMP-54F28 is efficacious as a single agent and in combination with standard of care in four hepatocellular carcinoma (HCC) and two ovarian cancer models. In the HCC models, OMP-54F28 shows tumor growth inhibition (TGI) as a single agent (average of 78%, p<0.05 vs. control) and displays additive TGI in combination with Sorafenib (average of 78%, p<0.05 vs. Sorafenib alone). Also, in the ovarian cancer models, treatment with OMP-54F28 results in TGI as a single agent (average of 32% vs. control) and shows additive TGI in combination with Paclitaxel (average of 79%, p=0.05, 48% with Paclitaxel alone). We also performed in vivo xenograft assays and found that OMP-54F28 as a single agent in combination with standard of care reduces tumor-initiating cell frequency in both HCC and ovarian cancer xenografts. The anti-tumor effect was associated with a decrease in cell proliferation, induction of cell differentiation, and modulation of target Wnt signaling.

INTRODUCTION

The Wnt/beta-catenin signaling pathway, which signals through the family of FZD receptors and several co-receptors, plays an important role in controlling cell differentiation, self-renewal, and maintenance of cancer stem cells. Aberrant activation of this pathway has been implicated in a number of human tumors including hepatocellular carcinoma (HCC), breast, ovarian, and pancreatic cancer.

OMP-54F28 is a first-in-class fusion protein consisting of the extracellular ligand-binding domain of the FZD8 receptor and the Fc domain of a human IgG1 antibody. OMP-54F28 binds Wnt ligands and prevents them from binding to FZD receptors.

The objective of our studies is to evaluate the efficacy of OMP-54F28 in treating minimally passaged patient-derived xenograft models of HCC and ovarian cancer.

MATERIALS AND METHODS

The recombinant fusion protein OMP-54F28 was generated at OncoMed Pharmaceuticals, Inc.

The tumor biopsies were provided from National Disease Research Institute (LIV1), Molecular Response (LIV4, LIV9), and Duke Cancer Institute (TIC), Duke University Medical Center. Tumor xenografts were initiated and propagated at OncoMed Pharmaceuticals, in NOD SCID mice.

For the ovarian efficacy models, tumors were implanted into the mammary fat pad of NOD SCID mice. Tumors were allowed to grow to ~150 mm³ and were treated with a control antibody (45 mg/kg, q2w), OMP-54F28 (25 mg/kg, q2w), Paclitaxel (15 mg/kg, q2w), and implanted into new recipient mice at varying cell numbers.

For the HCC efficacy models, tumors were implanted subcutaneously or orthotopically (liver) in nude or NOD SCID mice. For the subcutaneous models, implanted tumors were allowed to grow to a tumor size of ~150 mm³. For the orthotopic model, mice were randomized to receive either OMP-54F28 (25 or 50 mg/kg, q2w), Sorafenib (25 or 50 mg/kg, q2w), or the combination of OMP-54F28 and paclitaxel (combos).

For the HCC efficacy models, tumors were implanted subcutaneously or orthotopically (liver) in nude or NOD SCID mice. For the subcutaneous models, implanted tumors were allowed to grow to a tumor size of ~150 mm³. For the orthotopic model, mice were randomized to receive either OMP-54F28 (25 or 50 mg/kg, q2w), Sorafenib (25 or 50 mg/kg, q2w), or the combination of OMP-54F28 and paclitaxel (combos).

In the tumorigenicity and limiting dilution assays, tumors were harvested from the experimental efficacy groups, dissociated into single cell suspensions, counted, and implanted into new recipient mice at varying cell numbers.

To quantify gene expression, tumors were snap-frozen and RNA was isolated. cDNA was prepared and RT-PCR was performed using gene-specific human primers.

RESULTS

OMP-54F28 in Combination With Sorafenib Delineates Tumor Growth and Decreases Tumorigenicity in the OMP-LIV4 HCC Node Model

Figure 1. Effect of OMP-54F28 (50 mg/kg, s.c.) and Sorafenib (25 mg/kg, s.c.) combination on tumor growth inhibition (A) and tumorigenicity (B) in the OMP-LIV4 HCC node model. A: The tumor biopsies were provided from National Disease Research Institute (LIV1), Molecular Response (LIV4, LIV9), and Duke Cancer Institute (TIC), Duke University Medical Center. Tumor xenografts were initiated and propagated at OncoMed Pharmaceuticals, in NOD SCID mice. B: Tumorigenicity assay using limiting dilution assay. For the ovarian efficacy models, tumors were implanted into the mammary fat pad of NOD SCID mice. Tumors were allowed to grow to ~150 mm³ and were treated with a control antibody (45 mg/kg, q2w), OMP-54F28 (25 mg/kg, q2w), Paclitaxel (15 mg/kg, q2w), and implanted into new recipient mice at varying cell numbers.

• The Wnt pathway inhibitor OMP-54F28 is effective in promoting tumor growth inhibition when used in combination with either Sorafenib or Paclitaxel in treating patient-derived xenograft models of HCC and ovarian cancer.

• Tumorigenicity assays based on serial transplantation showed that OMP-54F28 is effective in reducing the tumor cell initiating frequency in patient-derived xenograft models of HCC and ovarian cancer.

• These findings provide a rationale for targeting the Wnt/beta-catenin pathway as a therapeutic approach in treatment of HCC and ovarian cancer.