**ABSTRACT**

Ovarian cancer is the deadliest gynecologic malignancy and the fifth leading cause of death from cancer in women in the U.S. The Wnt(β-catenin) pathway, which signals through the Frizzled (FZD) receptor family and several co-receptors, has long been implicated in cancer. We have developed ipafricept (FZD8-Fc, OMP-54F28), a recombinant fusion protein consisting of the ligand-binding domain of FZD8 and a human IgG1 Fc fragment. This fusion protein blocks Wnt signaling induced by multiple Wnt family members by binding and sequestering WNT.

Using minimally passaged ovarian patient-derived xenograft tumors (PDX), we demonstrate that ipafricept is efficacious in combination with chemotherapy in ovarian cancer. Utilizing an in vivo serial transplantation assay, we quantified a reduction of the tumor initiating cell frequency by ipafricept in combination with paclitaxel. Additionally, we have discovered that pre-treatment with ipafricept several days prior to paclitaxel therapy enhances the activity of both agents when compared to delivering the drugs simultaneously.

The anti-tumor effect observed is directly associated with a modulation of Wnt pathway gene sets. In responsive tumors, we discovered that a large number of WNT target genes were significantly down-regulated by ipafricept (e.g. AXIN2, LRP5/6, and FZD8). Conversely, in non-responsive tumors, these genes were either unchanged or up-regulated by the combination therapy. Histologic analysis revealed that total β-catenin protein levels were reduced by ipafricept alone and in combination with paclitaxel in responsive tumors but were unchanged in non-responsive tumors. We are using these tumors to develop biomarkers that can be used clinically.

These data demonstrate the potential therapeutic benefit of targeting Wnt signaling in ovarian cancer. A Phase 1b clinical trial is currently examining ipafricept in combination with paclitaxel and carboplatin in patients with recurrent platinum-sensitive ovarian cancer.

**RESULTS**

Ipafricept blocks Wnt ligands and prevents them from binding to FZD receptors.

**WNT Signaling Molecule LEF1 Modulated by Ipafricept in Responsive Tumors**

**Ipafricept Reduces the Cancer Stem Cell Frequency in Ovarian Cancer**

**Combinatorial Treatment Enhanced by Antagonizing the WNT Pathway with Ipafricept Prior to Taxanes**

**SUMMARY**

1. A subset of ovarian patient-derived xenograft tumors are responsive to the Wnt antagonist ipafricept and combination of ipafricept with Taxol.
2. Responsive tumors have reduced levels of WNT target genes post-therapy.
3. Ipafricept reduces expression of WNT signaling molecule LEF1 and reduces the ovarian cancer stem cell frequency.
4. Anti-tumor activity of ipafricept is enhanced by pre-dosing ipafricept prior to Taxol.
5. Targeting the WNT pathway in ovarian cancer may benefit a subset of patients.