Gilead: Betting Big on Simtuzumab with Phase II Studies Ongoing in Six Indications for Cancer and Fibrotic Diseases; However Targeting LOXL2 in Cancer May Face Significant Hurdles

Simtuzumab targets LOXL2, an enzyme involved in collagen remodeling. The drug is being tested in several cancers but also in idiopathic pulmonary fibrosis (IPF) and fibrosis associated with non-alcoholic steatohepatitis (NASH), two indications with high unmet need. These two indications have recently caught investors' attention as Intercept (ICPT) and InterMune (ITMN) have enjoyed explosive ~500% and ~170% market cap growth respectively after the announcement of positive results in NASH and IPF. Should animal model data for simtuzumab be recapitulated in the clinic, our expert consultants believe this drug could complement ICPT's and ITMN's agents in the respective diseases. Beyond the potential utility of simtuzumab in combination with other anti- cancer agents in Gilead's pipeline, it is not implausible that the company may deploy some of the substantial near term cash inflows towards acquiring smaller players such as ICPT or ITMN to better position themselves in fibrotic diseases.

Gilead is betting big on simtuzumab, phase II studies ongoing in six indications. The company obtained the rights to simtuzumab (formerly GS-6624/AB0024) with the acquisition of privately held Arresto Therapeutics in December 2010. The humanized anti-LOXL2 antibody simtuzumab had demonstrated promising anti-tumor and anti-fibrotic efficacy in preclinical models. As Gilead took over simtuzumab development, the oncology program started by Arresto was expanded to three phase II studies in pancreatic and colon cancer and in myelofibrosis. Additional randomized double blind phase II studies are testing this antibody in fibrotic diseases (idiopathic pulmonary fibrosis, advanced fibrosis associated with non-alcoholic steatohepatosis and primary sclerosing cholangitis, PSC) and in patients with liver fibrosis caused by HIV/HCV coinfection. This broad phase II program is targeting enrollment of ~1,700 patients, suggesting that Gilead has a high level of confidence in the potential of this product.

Simtuzumab appears best suited to development in fibrotic diseases rather than cancer indications. The rationale of targeting LOXL2 in fibrosis is that this enzyme functions as a key mediator of collagen cross-linking. Targeting the collagen cross-linking mechanism may help clear fibrotic tissue in liver, bile duct or lung. Our expert consultants believe that this approach may be complementary to other therapies currently in development (such as ITMN's Esbriet in IPF or ICPT's obethicolic acid in NASH). Gilead may get an early read into the activity of simtuzumab in NASH patients with advanced liver fibrosis or cirrhosis and in patients with PSC as the primary endpoint of these three phase II studies is change in collagen levels as measured by biopsy. According to management's guidance, the two NASH studies are expected to complete enrollment by mid-2014 and report out before mid-2015.

Targeting LOXL2 in cancer may face significant hurdles. LOXL2 is abundantly present in the microenvironment that surrounds tumor cells known as stroma, in colorectal, pancreatic and gastric cancers. Its collagen-modifying properties are hijacked to remodel the tumor environment and help promote the survival of cancer cells. High levels of LOXL2 are generally associated with a higher propensity for metastasis, higher tumor grade and poorer prognosis of these cancers. However, our expert consultants believe that inhibition of LOXL2 may be offset by de novo activation of other alternative pathways. Based on the scientific literature and this opinion, our outlook about the likely efficacy of simtuzumab in pancreatic and colon cancer is tepid at best. **Our advisers suggest that the product is much better suited for development in cancers where clinical manifestations are linked to fibrotic progression, such as myelofibrosis or neuroectodermal gastronintestinal tumors.** A phase II study of simtuzumab +/- Jakafi is ongoing in myelofibrosis. Should simtuzumab demonstrate any signs of activity in MF in combination with Jakafi, it is likely that Gilead may move on to test in combination with their in-house JAK agent, momelotinib. We expect initial data for this combination to report out at ASH in December 2014.

Source: Bernstein Research/Porges, March 6, 2014
Oncology Indication: Multiple
Keyword: Clinical Trials/Pipeline