FPA144: A Therapeutic Antibody for Treating Patients with Gastric Cancers Bearing FGFR2 Gene Amplification

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ABSTRACT

A subpopulation of patients with gastric cancer have an amplification of the receptor tyrosine kinase fibroblast growth factor receptor 2 (FGFR2) gene. The amplification is most common in the diffuse type of gastric cancer and its presence correlates with poor patient prognosis. Although it has been reported that there is high expression of FGFR2 protein in patients with the amplification, it is unknown which of the two major FGFR2 isoforms, FGFR2b or FGFR2c, is expressed. In this study we demonstrate by both quantitative PCR (qPCR) and immunohistochemistry (IHC) using FGFR2b specific antibodies, that it is the FGFR2b isoform, and not FGFR2c, that is overexpressed in gastric cancer tumors that contain the FGFR2 amplification.

FivePrime Therapeutics has developed an FGFR2-specific antibody, FPA144, to treat patients with gastric cancers bearing amplification of the FGFR2 gene. FPA144 is glycoengineered for enhanced antibody-dependent cell-mediated cytoxic activity (ADCC). FPA144 causes tumor growth inhibition by 72% in FGFR2 amplified gastric cancer xenograft models with FGFR2b amplification. In the SNU-16 model, FPA144 reduces the levels of FGFR2b protein expressed in the tumors by approximately 50%, and decreases both FGFR2b phosphorylation and autophosphorylation of the downstream effectors, FRS2. The anti-tumor effect of FPA144 is specific for gastric cancer xenograft model. Since this molecule, unlike the FGFR tyrosine kinase inhibitors, blocks signaling by only the FGFR2b and not the other FGFRs, we expect a favorable toxicity profile, either alone or in combination with chemotherapeutic agents. We anticipate starting clinical trials of FPA144 by the end of 2014.

BACKGROUND

• Gastric cancer is the second leading cause of cancer death worldwide.
• The fourth most common malignancy in the world.
• More than 90% of gastric cancer cases occur in Eastern Asia.
• Cumulative data indicate FGFR2 gene amplification occurs in approximately 5% of gastric cancer patients.
• FGFR2 gene amplification or FGFR2 protein over-expression is associated with lower survival in gastric cancer patients.

FGFR2 RNA SPLICING GENERATES THE FGFR2B ISOFORM

• FGFR2, FGFR2b and FGFR2c undergo alternative splicing that results in b and c isoforms of the receptor.
• The b isoform is restricted to epithelial lineages and the c isoform is preferentially expressed in mesenchymal lineages.
• FGFR2 RNA splicing in the third exon domain generates the FGFR2b isoform.

ENGINEERED TO DIRECTLY KILL TUMOR CELLS VIA ENHANCED ADCC

• Blocks FGFR2b-receptor activation.
• Down-regulates FGFR2b receptor levels.
• Causes tumor regression in animal models.
• Lead indication is FGFR2b-overexpressed gastric cancer.
• Companion diagnostic will identify patients most likely to respond to targeted treatment.

Tumors are sensitive to FGFR2b signaling in gastric cancer patient samples that exhibit FGFR2b amplification and strong FGFR2b IHC staining also show over-expression of FGFR2b mRNA.

REFERENCES


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