ABSTRACT #TPS260

Five Prime Therapeutics Inc.
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Enrolling a Rare Patient Population: Establishing Proof of Concept for FP-1039, an FGF "Trap," in Endometrial Cancer Patients with the S252W *FGFR2* Mutation

FivePrime™

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INTRODUCTION

FP-1039 Background

- The Fibroblast Growth Factor (FGF) / Fibroblast Growth Factor Receptor (FGFR) signaling pathway has been widely implicated in the development and maintenance of many different cancers
- FP-1039 is a soluble fusion protein consisting of the extracellular domains of human FGFR1 linked to the Fc region of human Immunoglobulin G_1 (IgG_1) (**Figure 1**)
- FP-1039 is designed to bind multiple FGF ligands and prevent them from activating multiple FGF receptors
- FP-1039 has multiple potential mechanisms of action in cancer:
  - Direct anti-tumor activity in cancers dependent on the FGF pathway
  - Inhibition of tumor angiogenesis
  - Inhibition of cancer stem cell maintenance
- FP-1039 is currently in a Phase I clinical study to characterize safety and pharmacokinetics in cancer patients[1]

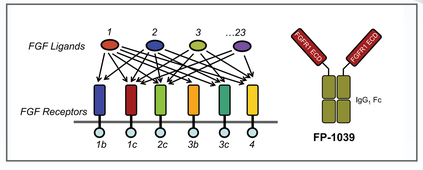

Figure 1. Targeting the FGF/FGFR Pathway with FP-1039. The FGF axis contains 4 FGF receptors with multiple splice forms and 22 FGF family ligands. There is selective binding of overlapping sets of ligands to the different receptors. FP-1039 is a soluble fusion protein consisting of the extracellular domains of human FGFR1 linked to the Fc region of human Immunoglobulin G_1 (IgG_1). It is designed to bind and sequester multiple FGF ligands and block activation of multiple FGF receptors. Previous data have demonstrated that FP-1039 is capable of blocking tumor growth in murine and human preclinical tumor models[2].

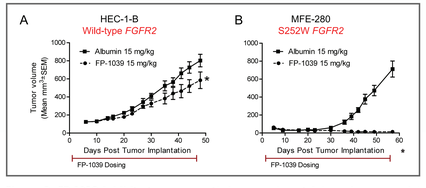

Figure 2. FP-1039 Inhibits tumor growth in an endometrial carcinoma model expressing S252W FGFR2. Efficacy of FP-1039 in a HEC-1-B (A) and MFE-280 (B) human endometrial cancer xenograft model. Five million HEC-1-B or MFE-280 cells were implanted subcutaneously over the right flank of SCID mice (N=10 per group). FP-1039 or albumin was administered intra-peritoneally twice a week at a dose of 15 mg/kg. * indicates *P* <0.01 as determined by t-test of area-under-the-curve.

Rationale for FP-1039 in Endometrial Cancer

- Germline mutations in the extracellular domain of FGFR2 are responsible for Apert syndrome, a congenital human skeletal disorder
- The same mutations have been found in endometrial carcinomas, among other *FGFR2* mutations:
  - 12-16% of primary endometrioid tumors have a *FGFR2* mutation
  - The Apert (S252W/P253R) *FGFR2* mutations are the most common, occurring in 7-10% of endometrial carcinomas[3, 4]
- Structure-function studies demonstrate that S252W FGFR2 has inappropriate, but ligand dependent activation. The mutant receptor:
  - Responds to ligands to which wild-type FGFR2 does not
  - Binds ligands with higher affinity than wild-type FGFR2
- These data suggest that some endometrial carcinomas are driven by activating *FGFR2* mutations:
  - In preclinical models, endometrial tumors with S252W mutations are more sensitive than wild-type to FP-1039[5] (**Figure 2**)
  - A simple predictive biomarker (presence of S252W or P253R mutation in tumor sample) exists and a CLIA-certified test has been developed

Biological Hypothesis/Potential Clinical "Proof of Concept"

Hypothesis: Tumors containing the Apert syndrome S252W (or P253R) mutations in *FGFR2* will be sensitive to FGF ligand blockade by FP-1039

Because of the high predicted tumor sensitivity, treating patients harboring *FGFR2* S252W/P253R mutations with FGF-ligand trapping represents:

- A compelling biologic opportunity to demonstrate "proof of concept"
- A population which should demonstrate biologic activity (significant improvement vs historical controls in ORR or PFS at 6 months) with treating very few patients

Challenge:

- The overall population of recurrent and/or metastatic endometrial cancer is small (6000-8000/year incidence in the US)[6]
- The percentage of patients with endometrial cancer and the *FGFR2* S252W or P253R mutation is small (7-10%)

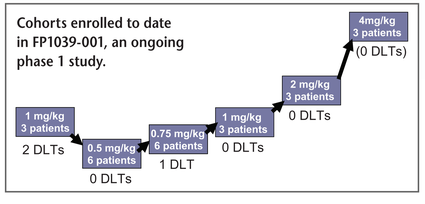

Figure 3. Summary of Phase 1 Clinical Trial for FP-1039. A standard "3+3" dose escalation approach is used. Dose limiting toxicities were encountered in the first cohort (1 mg/kg), however these DLTs were clinically disparate, not related to drug exposure and confounding factors were present. Four-fold higher doses have been administered without DLTs to date and dose escalation continues. A maximum tolerated dose (MTD) has not yet been determined nor has a clear AE profile. Preclinical data suggest a dose at or above 2 mg/kg inhibits tumor growth.

Trial Approaches

- Based on the incidence of endometrial cancer, recurrence rates, and the reported frequency of S252 or P253R FGFR2 mutations, it is estimated that there are ~500 US patients annually who may qualify for therapy with FP-1039 and therefore, ~200 patients must be screened to identify and treat 7-10 patients
- To provide a result in a meaningful time frame (12-18 months), accrual must be complete within 9 months (~1 patient per month)
- Using a standard approach and assuming a screening rate of 0.5 patient/site/month, at least 40 sites would be required
- The vast majority of these sites would not actually enroll or treat any patients; therefore the time and expense of qualification, initiation, drug shipment, and site close out will add significantly to the cost of the study
- The standard approach to treating recurrent or metastatic endometrial cancer (systemic chemotherapy for 6-8 weeks) provides a time interval during which patients can have their tumors assessed for presence or absence of S252W or P253R mutations and site activation may also occur
- The ability to "pre-screen" patients during initial systemic treatment and the need for very few patients to clinically test the biological hypothesis present an opportunity to use a novel trial approach to a selected patient population in which the screening and treatment aspects of the trial are separated

Screening for FGFR2 Exon 7 Mutations in Endometrial Carcinoma Patients

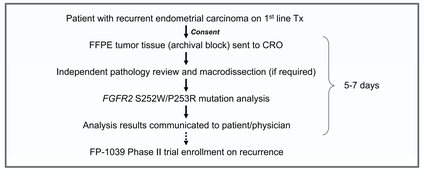

Figure 4. Summary of screening process. Patients can be referred to have their tissue blocks sent for analysis via their local physician. Analysis is performed at a central lab by a CLIA-certified process. If they are found to have the mutation, they may discuss the potential of participating in the treatment component of the trial with their local physician and consider participation in the treatment component of the trial.

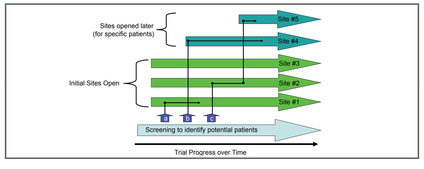

Figure 5. Our approach to efficiently treat subjects who are identified with the S252W mutation. In this example, sites geographically spread throughout the US have the protocol activated so that subjects may be treated. Subjects are identified via screening (Figure 4). Based on the timing of their identification and the logistics involved in opening a nearby site, several treatment possibilities exist: a) they may be treated at a currently active site for their entire treatment duration, b) they may be identified early enough so that a local site is active by the time they have disease progression and are eligible for FP-1039 treatment, or c) they may be transported to an open site for treatment and transfer their treatment once a local site is active. This approach should increase the likelihood that all participating sites enroll a patient and assure that all participating subjects are able to have treatment at a local site.

Trial Design: Single-Arm, Open Label, Phase 2, using Molecular Diagnostic for Patient Selection.

Primary Objectives

- Assess the objective response rate in patients with recurrent or metastatic endometrial cancer with *FGFR2* S252W or P253R tumor mutations when treated with FP-1039
- Assess the frequency of prolonged stable disease (as defined by percentage of patients alive and free from progressive disease at 6 months) in patients treated with FP-1039

Secondary Objectives

- Assess time to progression, median overall survival, and rate of one-year survival in patients treated with FP-1039
- Characterize the safety profile of FP-1039 in this patient population
- Characterize the pharmacokinetic and pharmacodynamic profiles in this patient population following FP-1039 administration

Major Inclusion Criteria

- Histologically confirmed endometrial cancer, locally advanced, recurrent, or metastatic
- Presence of *FGFR2* S252W OR P253R mutation confirmed by central lab
- ECOG Performance Status 0-2
- Measurable disease that has progressed since last treatment
- 0-2 prior treatment regimens for recurrent or metastatic disease
- No known or uncontrolled brain metastases

Major Exclusion Criteria

- Inadequate hematologic, renal, or hepatic function
- Prior therapy with an FGF-inhibitor
- Concurrent unstable disease that could jeopardize participation in study
- Concurrent active infection requiring antibiotics or other therapy
- No Risk factors for bevacizumab-associated bowel perforation

Study Treatment

- FP-1039 is administered intravenously over 30 minutes once a week (dose to be based on ongoing phase 1 study)

Assessments

- Safety: Adverse Events are assessed at each visit and graded by CTCAE v3.0
- Pharmacokinetics: Plasma samples are drawn for PK analysis at various time points after the first four infusions and after the eighth weekly infusion
- Pharmacodynamic (PD): selected PD sampling is performed pre-dose, Day 8, and Day 49 (after 8 weekly treatments)
- Immune Response: samples are taken for Immune response analysis on Days 1, 15, 49, and every 3 months thereafter while subjects continue to get treatment
- Efficacy: Tumor evaluation at baseline and every two months thereafter until disease progression

SUMMARY

- FP-1039 is an FGFR1:Fc fusion protein that binds multiple FGF ligands and prevents them from activating multiple FGF receptors
- S252W or P253R *FGFR2* mutant endometrial cancer is a population that provides an opportunity to demonstrate proof of concept for an FGF ligand "trap":
  - The ligand-dependent *FGFR2* mutations S252W or P253R are observed in endometrial cancer specimens at a frequency of ~7%[3, 4]
  - FP-1039 has single-agent therapeutic activity in mice with established human MFE-280 endometrial cancer xenografts bearing the S252W *FGFR2* mutation[6]
- FP-1039 is currently in a Phase I dose-escalation clinical study to characterize safety and pharmacokinetics in cancer patients
  - Exposures associated with activity in xenografts have been safely surpassed
- A *FGFR2* S252W and/or P253R CLIA-certified genomic mutation assay compatible with FFPE patient samples has been developed[5]
- A novel trial approach has been designed in which the screening and treatment aspects are separated. This approach allows efficient site activation for treatment after a rare potential patient has been identified
- As patients are identified, individual arrangements will be made to assure treatment is available:
  - Nearby site activation during the initial systemic chemotherapy for recurrent/metastatic disease thereby enabling FP-1039 treatment at the time of disease progression
  - Provision for travel to a main active site in short term as local site is activated

REFERENCES

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