Background

Five Prime Therapeutics, Inc. has developed an FGFR2b-specific humanized monoclonal antibody, FPA144, to treat cancer patients whose tumors overexpress FGFR2b. FPA144 blocks ligand binding and has been glyco-engineered to enhance antibody-dependent cell-mediated cytotoxicity. Preclinical models showed that FPA144 reprograms the tumor microenvironment by recruiting natural killer (NK) cells to the tumor, upregulating PD-L1 expression, and enhancing T cell infiltration [1]. FPA144 is currently in clinical development in gastric and urothelial cancers (UC). FPA144 completed dose escalation in a Phase 1 trial in patients with solid tumors and 3 mg/kg exhibited a durable complete response [2]. Five Prime evaluated FGFR2b expression in 387 archival primary UCs. We selected 32 cases with a wide range of FGFR2b expression to characterize baseline immune composition in the tumor microenvironment and their relationship with FGFR2b expression in UC patients to guide potential development of FPA144 in combination with other therapies.

Methods: IHC Assay Development

Tumor samples
- 32 archival primary UC cases (commercially sourced and selected to have a range of FGFR2b expression levels)
- FGFR2b expression - 62% were FGFR2b positive
- T stage at diagnosis - 72% were T1, 28% were T2

FGFR2b in Urothelial Cancer

FGFR2b H-scores positively correlate with tumor-infiltrating CD8, CD163, and PD-L1+ immune cells. From baseline immune composition and FGFR2b expression level, we clustered cases into three distinct groups: 1) Immune desert (low CD8+ T cells, tumor-associated macrophages (TAM), and PD-L1 expression in the whole tumor) with low or negative FGFR2b; 2) Immune excluded (high CD8+ T cells, TAM, and PD-L1 expression in tumor-associated stroma) with low to moderate FGFR2b; 3) Inflamed (high CD8+ T cells, TAM, and PD-L1 expression in the whole tumor) with moderate to high FGFR2b.

FGFR2b Expression and Baseline Immune Signature to Guide FPA144 Development in Urothelial Cancer

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Results: Urothelial Cancer FGFR2b-Immune Subtypes

FGFR2b H-scores positively correlate with tumor-infiltrating CD8, CD163, and PD-L1+ immune cells. From baseline immune composition and FGFR2b expression level, we clustered cases into three distinct groups: 1) Immune desert (low CD8+ T cells, tumor-associated macrophages (TAM), and PD-L1 expression in the whole tumor) with low or negative FGFR2b; 2) Immune excluded (high CD8+ T cells, TAM, and PD-L1 expression in tumor-associated stroma) with low to moderate FGFR2b; 3) Inflamed (high CD8+ T cells, TAM, and PD-L1 expression in the whole tumor) with moderate to high FGFR2b.

• Representative images of UC FGFR2b-immune subtypes

• FGFR2b high UCs have high CD8+ T cells, PD-L1+ immune cells, and proliferating cancer cells

• UC cases cluster into three groups based on FGFR2b expression and baseline immune signatures

Discussion & Conclusions

• The results from this selected subset of early stage (T1 and T2) UC patients (32 cases) suggest that FGFR2b is expressed in all immune subsets of UCs, but the expression level varies. The highest level of expression is in inflamed and more proliferative UCs.

• Five Prime will evaluate additional archival UC tissues from patients with more advanced metastatic disease to determine if there is an association of FGFR2b expression with baseline immune signature in late-stage patient tumors.

• We previously demonstrated FPA144 can “reprogram” the tumor microenvironment in a preclinical model with moderate FGFR2b expression [1]. FPA144 may perform a similar role in moderate and high expressing UC tumors to convert them into inflammatory tumors.

• Profiling FGFR2b expression and baseline tumor-associated immune cells could help guide the FPA144 clinical development strategy in UC patients.

• Currently, patients with metastatic UC are enrolling in the FPA144 clinical trial (#NCT02318329).

References