FPA144-001: A First in Human Study of FPA144, an ADCC-enhanced, FGFR2b Isoform-selective Monoclonal Antibody in Patients with Advanced Solid Tumors

#140

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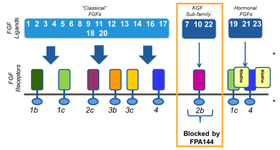
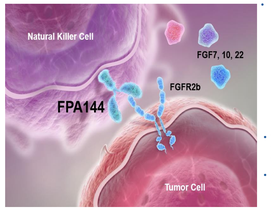
Background



- Fibroblast growth factors (FGFs) and their receptors play important roles in cellular proliferation, differentiation, migration and survival
- There are 22 known human FGFs and 4 FGF receptors (FGFR1–4). Alternative splicing of the third immunoglobulin-like domain of FGFRs1-3 produces two splicing variants, designated IIIb and IIIc, with distinct ligand binding specificity and tissue distribution (Turner, 2010)
- FGFR2b (also known as FGFR2IIIb, KGFR, or K-sam) binds to the KGF family of FGFs, with FGF7 and FGF10 being the most well characterized binding partners
- Tumors in 3–9% of patients with gastric cancer have amplification of the *FGFR2* gene that produces high levels of a splice variant derived protein called FGFR2b (Hattori, 1990; Hattori, 1996)
- Patients with *FGFR2* amplification have a poorer prognosis than patients without the amplification (Hattori, 1996; Han, 2015)
- *FGFR2* amplification is rarely found in gastric tumors that have amplification of *HER2*, *MET* or alterations in the KRAS pathway (Deng, 2012)

FPA144 Mechanism of Action



- FPA144 is a humanized IgG1 monoclonal antibody that binds selectively to the FGFR2b isoform of FGFR2
- FPA144 therapy is designed to deliver two distinct anti-tumor effects:
  1. FPA144 is glycoengineered[c] to enhance natural killer (NK) cell binding and stimulate an immune reaction against FGFR2b-expressing tumors through antibody-dependent cell-mediated cytotoxicity (ADCC)
  2. FPA144 inhibits ligand binding to FGFR2 and blocks receptor activation and downstream signalling (Gemo, 2014)
- The isoform specificity of FPA144 may improve tolerability and enable more complete target coverage relative to other approaches
- FPA144 does not inhibit FGF23 signaling and is therefore not expected to cause the dose-limiting hyperphosphatemia often associated with FGF receptor tyrosine kinase inhibitors
- FPA144 is being investigated as a potential therapy for patients whose gastric cancer overexpresses FGFR2b

*FPA144 is produced in a CHO cell line that lacks the *FUT8* gene, resulting in afucosylation

Patient Selection Strategy for Part 2

- **Immunohistochemistry (IHC) assay concurrently developed using proprietary FGFR2b antibody**
- **Overexpression of FGFR2b defined as IHC 3+ (defined as strong membranous staining of at least 10% of the tumor cells in a sample)**
- **Following IHC, all IHC 3+ samples will be subjected to FISH staining to determine the copy number of *FGFR2***

FGFR2b overexpression

IHC

* FPR2-D – proprietary FGFR2b antibody
Distinguishes FGFR2b and 2c
Commercial antibodies less specific
Validated by LabCorp

FGFR2 amplification

FISH

Positive - FGFR2 probe: centromere probe ≥2
Commercially available probes
Validated by LabCorp

*FPR2-D is a mouse monoclonal antibody that recognizes the same epitope as the therapeutic molecule FPA144

References

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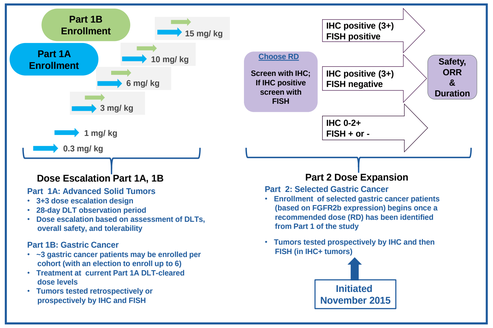
Turner N, Grose R. Fibroblast growth factor signaling: from development to cancer. Nat Rev Cancer. 2010; 10:116–29

Clinical Trial Design

- **A three-part, phase 1, open-label, safety, tolerability, and PK study (NCT 02318329) of ascending doses of FPA144 as monotherapy in the following cohorts of patients:**
  - Dose escalation portion in unselected solid tumor patients (Part 1A)
  - Dose escalation portion in gastric cancer patients (Part 1B)
  - Dose expansion portion in FGFR2b-selected gastric cancer patients (Part 2)
- **Eligibility Criteria:**
  - Key inclusion: Locally recurrent or metastatic disease that has progressed on or following standard treatment; ECOG performance status of 0 or 1
  - Key exclusion: Treatment with any anticancer therapy ≤ 14 days prior to first dose of FPA144; Prior treatment with any selective inhibitor of the FGF-FGFR pathway (Part 1B and Part 2 only)
- **FPA144 administered every 2 weeks in 4-week cycles until disease progression, unacceptable toxicity, patient or physician decision to discontinue, death or termination of the study**
- **Blood PK samples collected at pre-dose and at various time points throughout the study, including intensive sampling post first dose and collection of peak and trough in a subset of the following cycles**
  - FPA144 serum concentrations quantitatively measured by a validated ELISA method. PK parameters estimated for each subject with nominal dose, nominal infusion duration, and nominal sampling times using non-compartmental analysis (NCA) by WinNonlin
- **Data included herein are based on an interim analysis (cut-off date of October 29, 2015)**
  - Safety population includes 27 subjects enrolled and dosed with FPA144 in Parts 1A and 1B as of the cut-off
  - PK population includes 23 subjects with sample availability as of the cut-off

Study Design Overview



Study Results – Treatment Summary

- **27 patients enrolled and dosed with FPA144 (19 in Part 1A and 8 in Part 1B) as of October 29, 2015**
- **18 (94.7%) of 19 in Part 1A completed planned dosing of at least one cycle (and were DLT evaluable)**
- **14 of 19 patients enrolled in Part 1A have discontinued the study: 12 for reason of disease progression, one for lack of clinical benefit and one for inability to receive FPA144 infusion due to inclement weather**
- **All enrolled patients remain on study in Part 1B as of cut-off date**
  - **6 of 8 met the criteria for FGFR2b overexpression (IHC 3+ staining of ≥ 10% of tumor cells)**

Part 1A (Advanced Solid Tumors)				Part 1B (Gastric Cancer)			
Dose (mg/kg)	No. of Patients	Tumor Types	Mean Exposure (weeks)	Dose (mg/kg)	No. of Patients	Tumor Types	Mean Exposure (weeks)
0.3	3	breast, colon, neuroendocrine	24.2	0.3	0		0
1	4	colon, lung, gallbladder, submandibular	13.1	1	0		0
3	3	bladder, colon, gastric	13.6	3	1	gastric	14.0
6	3	2 colon, gastric	3.5	6	1	gastric	6.3
10	3	colon, gastric, peritoneal	4.2	10*	6	gastric	2.5
15	3	bile duct, esophagus, pancreatic	4.2	15	0		0
Total	19	12 Tumor Types	10.6	Total	8	All Gastric	4.4

* 2 of 6 patients in the 10 mg/kg cohort did not meet the criteria for FGFR2b overexpression (IHC-)

Baseline Patient Characteristics

	Part 1A (Dose Escalation, Advanced Solid Tumors)							Part 1B (Dose Escalation, Gastric)			
	FPA144 0.3mg/kg (N=3)	FPA144 1.0mg/kg (N=4)	FPA144 3.0mg/kg (N=3)	FPA144 6.0mg/kg (N=3)	FPA144 10mg/kg (N=3)	FPA144 15mg/kg (N=3)	FPA144 Total (N=19)	FPA144 1.0mg/kg (N=1)	FPA144 6.0mg/kg (N=1)	FPA144 10mg/kg (N=6)	FPA144 Total (N=8)
Age Median (yrs) (min, max)	74.0 (39, 76)	64.5 (37, 68)	63.0 (52, 75)	62.0 (47, 77)	64.0 (61, 80)	59.0 (32, 86)	63.0 (32, 86)	54.0	39.0	52.0 (40, 65)	49.5 (39, 65)
Female N (%)	1 (33.3)	2 (50.0)	0 (0)	1 (33.3)	2 (66.7)	2 (66.7)	8 (42.1)	1 (100)	0 (0)	3 (50.0)	4 (50.0)
Race N (%)											
White	3 (100)	4 (100)	3 (100)	3 (100)	3 (100)	3 (100)	19 (100)	0 (0)	0 (0)	1 (16.7)	1 (12.5)
Asian	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	1 (100)	5 (83.3)	7 (87.5)
BMI Median (kg/m²) (min, max)	28.7 (24.7, 41.3)	30.4 (24.6, 57.0)	24.5 (22.5, 24.9)	27.0 (26.3, 32.5)	24.6 (22.8, 25.5)	21.7 (19.4, 27.1)	25.5 (19.4, 57.0)	14.1	18.6	19.8 (14.8, 26.5)	18.3 (14.1, 26.3)
Prior Therapies Mean (No.) (min, max)	2.3 (2, 3)	4.3 (1, 8)	2.7 (1, 5)	4.0 (2, 6)	5.3 (3, 9)	1.3 (1, 2)	3.4 (1, 9)	2.0	6.0	2.5 (2, 3)	2.5 (2, 6)

Note: Includes subjects enrolled as of the cut-off date of October 29, 2015

Study Results – Safety Summary

As of the data cut-off of October 29th, 2015:

- **No DLTs in the dose-escalation (MTD not reached)**
- **No on-study deaths**
- **4 reported SAEs (across 2 subjects): ascites, large intestinal obstruction, pyrexia, and liver abscess**
- **No treatment-related SAEs reported**
- **No treatment-related AEs resulting in treatment discontinuation**
- **Of the 27 patients exposed to FPA144 in Parts 1A and 1B:**
  - **24 (89%) experienced a treatment-emergent AE (TEAE): 18 (95%) in Part 1A and 6 (75%) in Part 1B**
  - **16 (59%) experienced a TEAE assessed as related to treatment: 11 (58%) in Part 1A and 5 (63%) in Part 1B**

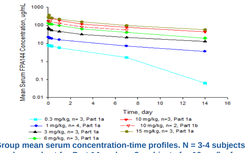
Most Common Treatment-related Adverse Events* (Incidence > 1 subject)

	Part 1A and Part 1B (Combined)			
Preferred Term	Grade 1	Grade 2	Grade 3/4	Total
Fatigue	3 (11.1)	4 (14.8)		7 (25.9)
Nausea	3 (11.1)			3 (11.1)
Diarrhea	2 (7.4)			2 (7.4)
Dizziness	2 (7.4)			2 (7.4)
Dry Eye	2 (7.4)			2 (7.4)
Keratitis	2 (7.4)			2 (7.4)
Lacrimation Increased	2 (7.4)			2 (7.4)
Pruritus	2 (7.4)			2 (7.4)
Vomiting	2 (7.4)			2 (7.4)

*Treatment relatedness is based on an assessment of possible or probable attribution to study drug by the investigator.

Study Results – Initial Pharmacokinetic Profile of FPA144

- **PK profile is typical of monoclonal antibodies with a short distribution phase and a long elimination phase**
- **Exposure increased slightly more than dose proportionally from 0.3 mg/kg to 1 mg/kg and approximately dose proportionally from 1 mg/kg to 15 mg/kg, suggesting target-mediated clearance**
- **Estimated elimination half-life by NCA in linear dose range was 1 to 2 weeks**
- **PK characteristics support once every other week or less frequent dosing**
- **The interpretation of any potential difference in clearance between gastric cancer and other cancer types is inconclusive from the limited data to date (cut-off of October 29, 2015)**



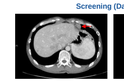
Group mean serum concentration-time profiles. N = 3-4 subjects per dose cohort for Part 1A and n = 2 subjects for 10 mg/kg for Part 1B. Each line represents group mean for one dose cohort with symbols indicated time points where data were collected.

Study Results – Preliminary Radiographic Responses in FGFR2b-selected Gastric Cancer Patients in Part 1B

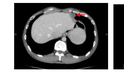
- **6 patients in Part 1B with FGFR2b overexpression**
- **Summary of tumor responses* (as of January 15, 2016) based on preliminary CT data obtained after the data cut-off of October 29, 2015:**
  - 2 Partial Responses (1 confirmed, 1 unconfirmed)
  - 3 Stable Disease (2 confirmed, 1 unconfirmed)
  - 1 Progressive Disease
- **Data are preliminary and subject to change**

Partial Response in Part 1B: Subject 605-1002 (6 mg/kg Cohort)

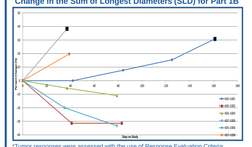
Screening (Day -14)



Cycle 4 Day 1 (Day 83)

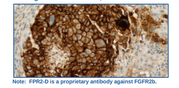


Change in the Sum of Longest Diameters (SLD) for Part 1B



*Tumor responses were assessed with the use of Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1

FPR2-D Staining of Adrenal Gland, Metastatic Adenocarcinoma

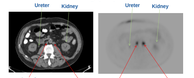


Note: FPR2-D is a proprietary antibody against FGFR2b.

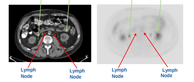
Study Results – Radiographic Response and Decreased FDG PET Uptake in a Patient with Urothelial Bladder Cancer (UBC)

- **76 year-old male presented with hematuria in July 2014 and diagnosed with Stage 4 UBC (T2, N2, M0)**
  - Resection of the primary tumor and 4 cycles of gemcitabine and cisplatin in the adjuvant setting
  - Significant retroperitoneal and para-aortic lymphadenopathy, metabolically active by PET, found on Day -5
  - Single measurable lymph node followed by CT (18 mm X 12 mm at Screening, Day -5)
  - Patient dosed in 3 mg/kg cohort on Day 0
  - Routine re-staging scans conducted approximately every 6 weeks
  - No appreciable lymphadenopathy (confirmed on subsequent scans) as of Day 123
  - CT scans on day 85 and day 165 show a confirmed PR by RECIST 1.1 criteria
  - PET (performed on Day 213) showed no metabolic activity in the initial tumor
  - Retrospective IHC revealed IHC2+ status
- **The patient currently continues on therapy (277 days as of January 15, 2016)**

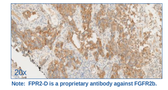
Screening (Day -5)



Cycle 8 Day 15 (Day 213)



FPR2-D Staining of Urothelial Transitional Cell Carcinoma



Note: FPR2-D is a proprietary antibody against FGFR2b.

Conclusions

- **FPA144 was well tolerated in doses up to 15 mg/kg in patients with advanced solid tumors**
  - No DLTs or MTD were observed during Part 1
  - The most common FPA144 treatment-emergent toxicities were Grade 1 or 2 and self-limited
  - The overall safety profile of FPA144 appears different from small molecule kinase inhibitors that target FGFR2 (for example, no hyperphosphatemia was seen with FPA144)
- **FPA144 has saturable, nonlinear clearance and is able to support once every other week or less frequent dosing schedule**
- **Confirmed and unconfirmed radiographic responses in patients with FGFR2b-selected gastric cancer (based on preliminary data obtained after the initial presentation data cut-off) support further clinical investigation of FPA144 in gastric cancer**
- **Confirmed radiographic and metabolic response observed in a urothelial bladder cancer patient suggests further exploration of the potential for FPA144 therapy in additional cancer settings and the IHC2+ finding in this subject may help inform approaches to patient selection**
- **Enrollment of FGFR2b-selected gastric cancer patients in Part 2 is now underway at the recommended dose of 15 mg/kg**

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