A phase 1, multicenter, dose-escalation study of PRN1371, an irreversible covalent FGFR1-4 kinase inhibitor, in patients with advanced solid tumors including metastatic urothelial carcinoma (mUC)

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Introduction

Multiple human cancers harbor alterations in FGFRs that drive tumor growth, including mutations, fusions and amplifications. There is mounting data from many Phase 1 and 2 studies conducted with various FGFR inhibitors demonstrating encouraging utility of this target for the treatment of cancers that harbor various FGFR alterations across a broad range of tumor types. Most recently, the kinase inhibitor erdafitinib was approved for treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC) that has FGFR2 or FGFR3 genetic alterations that have progressed on at least one line of platinum-containing chemotherapy. The incidence of FGFR activating mutations, translocations, or fusions in urothelial cancer is reported to be approximately 20%.[1] It is notable that the level of FGFR mutations varies depending on grade and staging of cancer. For example, in non muscle invasive bladder cancer (NMIBC) the frequency increases to >50% of patients.

PRN1371 is a potent, covalent, highly selective FGFR1, 2, 3 and 4 inhibitor, which targets a cysteine residue within the kinase domain.[2] This approach enables highly selective (Figure 1, Tables 1 & 2) and sustained inhibition of FGFR without the necessity to maintain systemic exposure of the drug. The dose escalation (part A) portion of a Phase 1 open-label study of PRN1371 in adult patients with advanced solid tumors has been completed and results reported. The cohort expansion (part B) portion of the study evaluating mUC patients with FGFR1, 2, 3, or 4 alterations is currently ongoing.

Figure 1. Graphical representation of PRN1371 kinase selectivity against 250 kinases at 1 mM

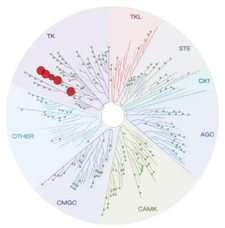


Table 1. Biochemical IC50s.

Kinase	IC50 (nM)
FGFR1	< 1
FGFR2	1
FGFR3	4
FGFR4	20
VEGFR	>500

Table 2. Cell proliferation in Ba/F3 cells transfected with wild type or mutant FGFR and cancer cell lines harboring FGFR alterations. PRN1371 maintains cellular potency against multiple FGFR alterations.

Ba/F3 Cells IC50 (nM)		Cell proliferation IC_{50} (nM)	
FGFR1	< 1	SNU16 (FGFR2 amp)	3
FGFR2	< 1	RT4 (FGFR3:TACC3)	4
FGFR3	2	RT112 (FGFR3:TACC3)	4
FGFR4	50	Hep3B (FGFR4; FGF19)	6

Trial Design

3 + 3 Design
- Intra-patient dose-escalation permitted to one level below the actively enrolling level.
- Patients may continue on study until they experience either progressive disease, intolerable toxicity, or no further benefit from study therapy.
- Prophylactic phosphate binders allowed for Cohorts 2 - 6
- CT/MRI scan at screening and every 2 cycles

Figure 2. Dose Cohorts

Primary Endpoints
- Incidence of dose limiting toxicities to evaluate maximum tolerated dose (MTD) and maximum administered dose (MAD)
- Incidence of treatment emergent adverse events
- Clinical response rate: objective response rate (ORR), progression-free survival (PFS), and duration of response (DOR) using RECIST criteria, Version 1.1

Secondary Endpoints
- Pharmacokinetics
- Changes in serum phosphate, FGF23

Exploratory Endpoints
- Evaluate the relationship of FGFR genetic alteration status and response
- Evaluate the relationship between biomarkers in tumor biopsies taken pre- and post-treatment and 1) the clinical efficacy of PRN1371 and 2) any pharmacodynamic relationship with PRN1371 treatment

Key Inclusion Criteria
- Age ≥ 18 years
- Patients metastatic or recurrent solid tumors
- Failed 1st-line systemic treatment
- If indicated, failed approved 2nd-line therapy
- No standard therapy options
- Evaluable, progressive, and measurable disease per RECIST 1.1
- ECOG PS ≤ 1

Key Exclusion Criteria
- Prior treatment with a highly selective FGFR inhibitor > 8 weeks

PK Results

- Rapid absorption with mean Tmax ranging from 1.00 to 1.5 hours
- Short half-life with mean T1/2 ranging from 1.42 to 2.15 hours
- Systemic exposure appeared to increase proportionally over the dose range tested
- Accumulation following multiple dosing and between QD and BID dosing appeared to be minimal with high variability and slightly higher following BID dosing

Figure 3. PRN1371 exposure

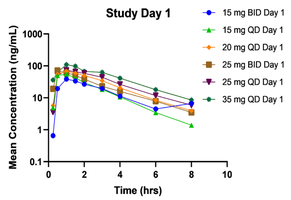


Table 3. PRN1371 exposure

Dose Group	Tmax (h)	Cmax (ng/mL)	AUCinf (ng*h/mL)	T1/2 (h)
15mg QD	1.00	61.0	134	1.42
20 mg QD	1.50	81.8	216	1.63
25mg QD	1.00	90.6	255	1.61
35mg QD	1.50	126	487	2.15
15mg BID	1.31	44	109	1.56
25mg BID	1.00	86	191	1.46

Median reported for t_{max} (h). Arithmetic mean reported for $t_{1/2}$ (h). Geometric mean reported for C_{max} (ng/mL), AUC (ng*h/mL).

PRN1371 urine concentration

Overall fraction of drug recovered in urine over 8 hours reached levels well in excess of cellular IC90.

Table 4. PRN1371 urine concentration

QD Dose Cohort	PRN1371 Urine Concentration ng/ml (±SD)	Fold above cellular IC90
15 mg (n=3)*	59 (±9)	12x
20 mg (n=3)	150 (±141)	30x
25 mg (n=7)	114 (±70)	23x
35 mg (n=7)	211 (±192)	42x

* Excluding one outlier (900 ng/ml)

Safety

Overall, PRN1371 was generally well tolerated up to a maximum dose of 35mg QD. During the course of study, the dose for three subjects escalated from an initial dose of 25mg QD to 35mg QD. With twice daily dosing, insufficient numbers of patients were evaluable to assess for tolerability at either 25mg BID or 15mg BID dose group due to receiving <90% of doses in the first treatment cycle. In several cases doses were reduced to either 35mg QD or 10mg BID and patients remained on study. Treatment related TEAEs in 5 patients led to study discontinuation. Two patients remained on treatment at time of data cutoff (at cycles 16 and 23) and were receiving 25mg of PRN1371 once daily. A maximum tolerated dose was not determined and the dose of 35mg QD was identified for the cohort expansion phase.

Table 5. Number of patients reporting TEAEs

All TEAEs Category (N, %)	Max Dose 15 mg QD (N=4)	Max Dose 20 mg QD (N=4)	Max Dose 25 mg QD (N=4)	Max Dose 35 mg QD (N=10)*	Max Dose 25 mg BID (N=8)	Max Dose 15 mg BID (N=6)	Total (N=36)
All TEAEs							
Any grade	4 (100%)	4 (100%)	4 (100%)	10 (100%)	8 (100%)	5 (83.3%)	35 (97.2%)
Grade ≥ 3	2 (50.0%)	1 (25.0%)	1 (25.0%)	5 (50.0%)	5 (62.5%)	4 (66.7%)	18 (50.0%)
Serious	2 (50.0%)	1 (25.0%)	1 (25.0%)	5 (50.0%)	3 (37.5%)	4 (66.7%)	16 (44.4%)
PRN1371-related TEAEs							
Any grade	4 (100%)	3 (75.0%)	3 (75.0%)	7 (70.0%)	8 (100%)	4 (66.7%)	29 (80.6%)
Grade ≥ 3	0	0	0	1 (10.0%)	4 (50.0%)	3 (50.0%)	8 (22.2%)
Serious	0	0	0	1 (10.0%)	2 (25.0%)	2 (33.3%)	5 (13.9%)
TEAE Leading to Study Discontinuation	1 (25.0%)	0	1 (25.0%)	1 (10.0%)	1 (12.5%)	1 (16.7%)	5 (13.9%)

*Includes 3 patients who dose escalated from 25mg QD cohort

Side effects observed in >10% of patients are reported in Table 6. The most common TEAE observed was hyperphosphatemia, which is an expected on target effect of pan-FGFR inhibition and occurred in ~67% of patients. Subsequent to the first cohort administered, patients were recommended prophylactic use of phosphate binding agents (sevelamer). FGFR inhibition has been associated with events of central serous retinopathy (CSR). Three events of CSR (Grade 1) and 1 event of retinopathy (Grade 3; 15 mg BID) occurred in 3 patients during treatment with PRN1371. All cases occurred in patients originally administered PRN1371 twice daily, though in 3 of 4 cases the dosing frequency had been reduced to once per day prior to the time of onset. The median time of onset was approximately 83 days.

Table 6. Treatment related adverse events in >10% of patients

Preferred term	Max Dose 15 mg QD (N=4)	Max Dose 20 mg QD (N=4)	Max Dose 25 mg QD (N=4)	Max Dose 35 mg QD (N=10)*	Max Dose 25 mg BID (N=8)	Max Dose 15 mg BID (N=6)	Total (N=36)
Hyperphosphatemia	4 (100%)	2 (50.0%)	2 (50.0%)	7 (70.0%)	7 (87.5%)	2 (33.3%)	24 (66.7%)
Grade 3/4	0	0	0	0	3 (37.5%)	0	3 (8.3%)
Constipation	1 (25.0%)	2 (50.0%)	0	1 (10.0%)	3 (37.5%)	1 (16.7%)	8 (22.2%)
Dry Mouth	0	2 (50%)	1 (25.0%)	2 (20.0%)	1 (12.5%)	1 (16.7%)	7 (19.4%)
Nausea	0	1 (25.0%)	0	2 (20.0%)	0	3 (50%)	6 (16.7%)
Alopecia	0	0	1 (25.0%)	1 (10.0%)	2 (25.0%)	0	4 (11.1%)
Decreased appetite	0	2 (50.0%)	1 (25.0%)	1 (10.0%)	0	0	4 (11.1%)
Dysgeusia	0	1 (25.0%)	0	0	1 (12.5%)	2 (33.3%)	4 (11.1%)
Vomiting	0	1 (25.0%)	0	0	1 (12.5%)	2 (33.3%)	4 (11.1%)
CSR/Retinopathy	0	0	0	0	2 (25.0%)	1 (16.7%)	3 (8.33%)
Grade 3/4	0	0	0	0	0	1 (16.7%)	1 (2.8%)
Other ocular event**	1 (25.0%)	0	0	1 (10.0%)	3 (37.5%)	1 (16.7%)	6 (16.7%)

Includes 3 patients who dose escalated from 25mg QD cohort

***Other ocular events include blepharitis, cataract, dry eye, retinal detachment, trichomegaly, xerophthalmia*

Results

While the patient population for part A of the study was not designed for evaluation of response in a specific tumor type or FGFR alteration, patients were evaluated for response to PRN1371 at cycle 3 day 1. A designation of stable disease occurred in 11 of 36 patients (Figure 5). The best percentage change from baseline in target lesion sites for evaluable patients is summarized in Figure 4.

Figure 4. Summary of best responses

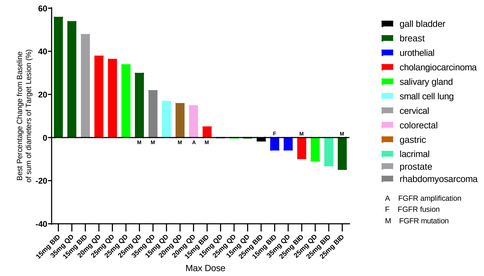
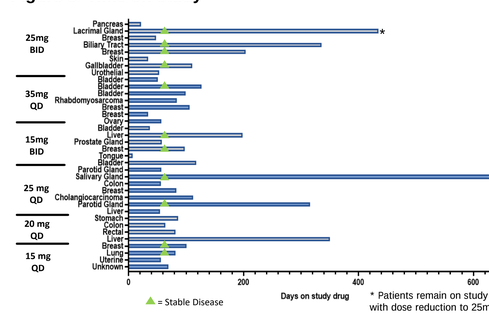


Figure 5. Time on study



Conclusions

- PRN1371 was generally well tolerated with hyperphosphatemia being the most frequently observed adverse event.
- PRN1371 exhibited rapid absorption and clearance, increased exposure with dose and measurable drug levels in urine.
- Evidence of stable disease was noted in 11 of 36 patients.
- The cohort expansion phase of the trial is currently enrolling patients with mUC at 35mg QD.

References

1. Helsten, T., et al. (2016). "The FGFR Landscape in Cancer: Analysis of 4,853 Tumors by Next-Generation Sequencing." Clin Cancer Res **22**(1): 259-267.
2. Venetsanakos, E., et al. (2017). "The Irreversible Covalent Fibroblast Growth Factor Receptor Inhibitor PRN1371 Exhibits Sustained Inhibition of FGFR after Drug Clearance." Mol Cancer Ther **16**(12): 2668-2676.