PRN1371, an irreversible, covalent inhibitor of FGFR1, 2, 3 and 4 is highly efficacious in preclinical tumor models

#1249

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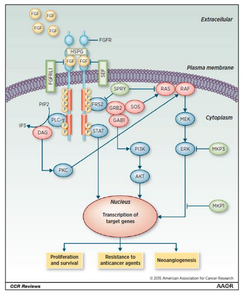
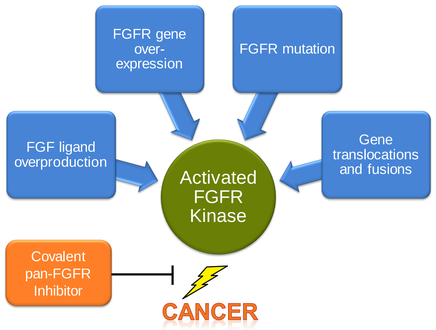
Introduction

Multiple human cancers harbor alterations in FGFRs that drive tumor growth, including mutations, translocations and amplifications. Recently, Phase 1 studies have demonstrated an encouraging utility of FGFR inhibitors for the treatment of FGFR-driven cancers. Challenges remain to identify FGFR inhibitors that do not have off-target inhibition, e.g. of VEGFR2, and that allow for strategies that translate into significant reduction of FGFR activity to improve clinical responses in patients while minimizing on-target toxicity.

We have developed a covalent, irreversible, highly selective FGFR1, 2, 3 and 4 inhibitor, PRN1371, by targeting a cysteine residue within the kinase domain. This approach enables highly selective and sustained inhibition of FGFR which extends well beyond circulating drug concentrations. PRN1371 is currently in a phase 1 clinical trial for the treatment of solid tumors.



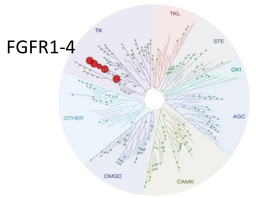
Touat et al., Clinical Cancer Research 2015



Results

PRN1371 is highly potent and selective FGFR inhibitor

Assay	PRN1371	BGJ398	AZD4547
Biochemical IC50 (nM)			
FGFR1	< 1	0.9	1.2
FGFR2	1	0.6	0.4
FGFR3	4	1.9	4.9
FGFR4	20	23	27
VEGFR	>500	141	37
250 kinase panel (# of kinases)			
90% inh @ 1 μM	5	5	14
50% inh @ 1 μM	14	19	62



Kinase selectivity profile of PRN1371screened against 250 kinases. Dots represent individual kinase with > 90% inhibition at 1 μM.

PRN1371 exhibits potent cellular activity

Assay	PRN1371	BGJ398	AZD4547
Transfected Ba/F3 IC50 (nM)			
FGFR1	< 1	5.8	27
FGFR2	< 1	7.5	11
FGFR3	2	7.4	37
FGFR4	50	261	289
VEGFR	>2000	>2000	>2000
Parental	>2000	>2000	>2000
HUVEC Primary Cells IC50 (nM)			
FGF-stim pERK	2	5	7
VEGF-stim pERK	> 5000	6310	290

Cellular activity was assessed in range of BaF/3 cells transfected with WT FGFR. Cellular potency on pERK was assessed in HUVEC cells stimulated with either FGF or VEGF.

PRN1371 maintains high potency against FGFR alterations

Assay	PRN1371	BGJ398	AZD4547
Transfected Ba/F3 IC50 (nM)			
FGFR2 WT	< 1	7.5	11
FGFR2 (K660E)	1	14	9.8
FGFR2 (K660N)	< 1	6.9	11
FGFR2 (N550K)	4	87	121
FGFR3 WT	2	7.4	37
FGFR3 (K650M)	3	45	133
Cell proliferation IC50 (nM)			
SNU16 (FGFR2 amp)	3	5	7
RT4 (FGFR3:TACC3)	4	184	230
RT112 (FGFR3:TACC3)	4	19	36
AN3CA (FGFR2 mut)	43.3	n/a	n/a
Hep3B (FGFR4; FGF19)	6	96	116
OPM2(FGFR3 transl)	14	n/a	n/a

Confirmation of prolonged occupancy

Enzymatic activity 24 hrs post equilibrium dialysis (% inhibition)

Assay	PRN1371	BGJ398	AZD4547
FGFR1	99%	67%	17%
FGFR2	99%	52%	7%
FGFR3	97%	0%	12%

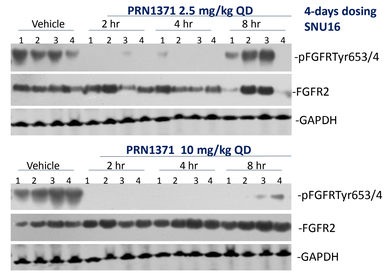
FGFR2 target occupancy in SNU16 cells treated with cycloheximide following washout

Time	PRN1371	BGJ398	AZD4547
0 hr	95%	75%	69%
1 hr	90%	15%	48%
4 hr	86%	21%	3%

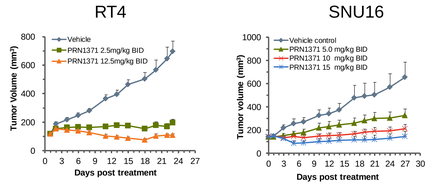
PRN1371 exhibits excellent preclinical safety pharmacology profile

- Cerep panel: No hits >50 % inhibition @ 10 μM
- hERG IC50: Free fraction provides >100x window over cellular IC90
- AMES: clean against 5 strains
- No ECG changes in a 4 week dog study at all doses tested

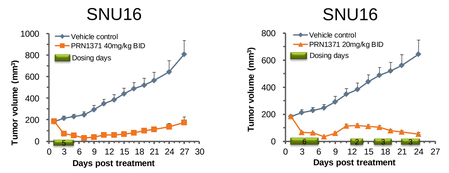
Sustained inhibition of pFGFR in SNU16-tumor bearing mice dosed with PRN1371



Efficacy observed in FGFR-altered xenograft models



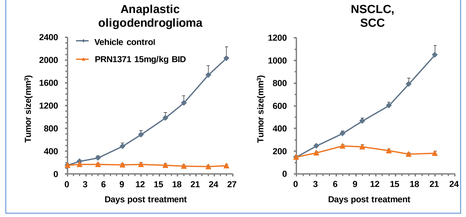
Efficacy maintained with intermittent dosing of PRN1371



Oral daily dosing of PRN1371 inhibits tumor growth in FGFR-driven xenograft models. Durable tumor regression is achieved after 5 days of dosing near MTD or with an intermittent schedule.

Efficacious responses in PDX models supports patient selection approach

PDX Type	FGFR alteration	Tumor growth inhibition (%)
Lung (NSCLC,SCC)	FGFR1 Amp + High Expr	96.1%
Lung (NSCLC, Adenocarcinoma)	FGFR1 Amp + High Expr	64.6%
Lung (NSCLC,SCC)	FGFR1 Amp + High Expr	59.5%
Lung (NSCLC,SCC)	FGFR3 Amp + High Expr	No response
Lung (NSCLC,SCC)	FGFR2 Amp	65%
Anaplastic oligodendroglioma	FGFR3:TACC Fusion	100.3% Regression (-3%)
Mixed liver	FGFR2:CCDC6 Fusion	>100% Regression (-76%)
Breast	FGFR2 Amp + High Expr FGFR2:GAB2 Fusion	61%



PRN1371 exhibits excellent preclinical safety profile

- Well tolerated with on-target class effect safety findings – including dose-dependent hyperphosphatemia, with concomitant tissue mineralization and bone changes at highest doses
- Currently in phase I clinical trial for treatment of solid tumors (NCT02608125)

Conclusions

- PRN1371 is an irreversible, covalent, selective inhibitor of FGFR1-4 exhibiting high potency against cancer cell lines harboring FGFR amplifications, mutations, and translocations
- Tumor regression in xenograft models was observed with daily or intermittent oral dosing and was well-tolerated
- FGFR-altered PDX models showed durable tumor growth inhibition and regression
- FGFR mediated hyperphosphatemia may be potentially managed with an intermittent dosing schedule that also maintains robust efficacy
- PRN1371 is currently in a phase I clinical trial for treatment of solid tumors (NCT02608125)