

Preliminary Results From a Phase 1/2 Study of INCB054828, a Highly Selective Fibroblast Growth Factor Receptor Inhibitor, in Patients With Advanced Malignancies (fight-101)

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Introduction

- Dysregulation of fibroblast growth factor receptor (FGFR) signaling can lead to the establishment and progression of cancer, and genetic alterations in *FGFR1*, *FGFR2*, and *FGFR3* have been described in many tumor types^{1,2}
- Results from early clinical studies of selective FGFR inhibitors have demonstrated clinical benefit in patients with tumors bearing *FGFR* alterations³⁻⁷
- INCB054828 is a potent and selective inhibitor of FGFR1, FGFR2, and FGFR3 *in vitro* and *in vivo*⁸
- In vivo*, once-daily oral administration of INCB054828 inhibited the growth of tumors that were dependent upon FGFR1, FGFR2, and FGFR3 activity at tolerated doses⁸
- This ongoing phase 1/2 study evaluates INCB054828 alone or combined with other agents for refractory advanced malignancies

Objective

- To evaluate the safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of INCB054828 for the treatment of patients with refractory advanced malignancies

Methods

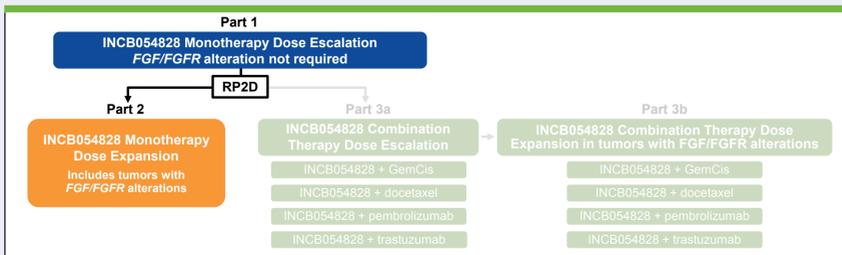
Patients

- ≥ 18 years of age, with life expectancy > 12 weeks
- Part 1 (monotherapy dose escalation): any advanced solid tumor (*FGF/FGFR* alteration not required)
- Part 2 (monotherapy dose expansion): malignancies with *FGF/FGFR* alteration
- Part 3a (combination dose escalation): advanced solid tumors for which treatment with gemcitabine + cisplatin, docetaxel, pembrolizumab, or trastuzumab is relevant
- Part 3b (combination dose expansion): advanced solid tumors with *FGF/FGFR* alteration for which treatment with gemcitabine + cisplatin, docetaxel, pembrolizumab, or trastuzumab is relevant
- Malignancies refractory to prior therapy, with no further effective standard therapy available, or the prescribed combination therapy is relevant (part 3 only)
- Eastern Cooperative Oncology Group performance status ≤ 1 (part 1) or ≤ 2 (parts 2 and 3)
- With archival tumor specimen or willingness to undergo a pretreatment tumor biopsy
- Patients with untreated brain or central nervous system (CNS) metastases or brain/CNS metastases that have progressed, or who have received selective FGFR inhibitors within the past 6 months are excluded

Study Design

- This is an ongoing, open-label, phase 1/2, 3-part study (NCT02393248; fight-101) of INCB054828 in adults with advanced malignancies (Figure 1)
- Patients receive INCB054828 orally once daily on a 21-day cycle (2-weeks on/1-week off)
- Part 1 determines the recommended part 2 dose (RP2D)
 - The RP2D is the lower of the maximum tolerated dose (defined as 1 dose level below that at which ≥ 33% of patients in a particular cohort report dose-limiting toxicities [DLTs]) or the pharmacologically active dose (PAD; defined as the dose at which ~67% of patients attain hyperphosphatemia) with or without prophylactic concomitant phosphate binders
- Multiple RP2Ds may be used moving into parts 2 and 3
 - In part 1, the first 3 cohorts (1–4 mg once daily) evaluate single patients and then a 3 + 3 design is used (6–20 mg once daily)
 - In part 2, patients with FGFR activation receive INCB054828 at the PAD (9 mg once daily) or RP2D (13.5 mg once daily); this regimen is also used in combination with standard therapies in part 3
- Hyperphosphatemia is managed with diet modification, phosphate binders, or dose modification

Figure 1. Study Design



This poster reports data from parts 1 and 2 of the study. GemCis, gemcitabine/cisplatin; RP2D, recommended part 2 dose.

Assessments

- Primary endpoints
 - Safety and tolerability
 - PD of INCB054828 (including serum phosphorus level)
- Secondary endpoints
 - Efficacy measured by tumor response rates in patients with measurable disease, as determined by investigator assessment of response (using RECIST v1.1, International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma, or Response Assessment Criteria for Subjects with Myeloproliferative Neoplasms)
 - PK (C_{max} , t_{max} , C_{min} , AUC_{0-24} , $t_{1/2}$, and CL/F)
- Exploratory endpoints
 - Efficacy measured by duration of response and progression-free survival (PFS)
 - Plasma and whole blood biomarkers and their correlation with overall response rate (ORR) and PFS
 - Tumor-specific gene alterations and gene expression profiles and their correlation with ORR and PFS
 - DLTs are assessed by the investigator using the current Common Terminology Criteria for Adverse Events v4.03 criteria
 - The current poster reports preliminary safety, efficacy, PK, and PD of INCB054828 monotherapy (parts 1 and 2)

Statistics

- All safety and efficacy analyses were performed on patients enrolled in the study who received at least 1 dose of study drug
- All analyses are exploratory only

Results

Patients

- As of the data cutoff (January 4, 2017), 49 patients (part 1, n = 22; part 2, n = 27) were treated with INCB054828 at doses ranging from 1 to 20 mg once daily; patient demographics and disease characteristics are presented in Table 1
- In part 1 (*FGF/FGFR* alterations not required), *FGF/FGFR* alteration was detected in 1/22 (5%) patient (data were not assessed/missing for 20 patients; 1 patient had no alteration)
- In part 2 (*FGF/FGFR* alterations required), 27/27 (100%) patients had *FGF/FGFR* alterations
 - Most common tumors were cholangiocarcinoma (n = 7), breast cancer (n = 4), esophageal cancer (n = 3), and ovarian cancer (n = 3)
- In parts 1 and 2, 30 (61%) patients discontinued treatment, due to disease progression (n = 21 [43%]), death (n = 4 [8%]), physician/patient decision (n = 3 [6%]), and other reasons (n = 2 [4%]; consent withdrawal, hospice admission); 19 patients remain on treatment

Table 1. Baseline and Demographic Characteristics

Characteristics	INCB054828 Monotherapy (part 1) (N = 22)	INCB054828 Monotherapy (part 2) (N = 27)	INCB054828 Monotherapy (parts 1 and 2) (N = 49)
Age, median (range), y	55 (21–77)	61 (34–77)	58 (21–77)
≤ 65 y	18 (82)	19 (70)	37 (76)
Men, n (%)	10 (45)	10 (37)	20 (41)
Race, n (%)			
White	20 (91)	22 (81)	42 (86)
Black	2 (9)	4 (15)	6 (12)
Other	0	1 (4)	1 (2)
ECOG performance status, n (%)			
0	7 (32)	8 (30)	15 (31)
1	15 (68)	19 (70)	34 (69)
Number of prior therapy regimens, n (%)			
1	21 (96)	25 (93)	46 (94)
2	0	4 (15)	4 (8)
≥ 3	3 (14)	6 (22)	9 (18)
≥ 3	18 (82)	15 (56)	33 (67)
FGF/FGFR alteration			
Yes	1 (5)	27 (100)	28 (57)
No	1 (5)	0	1 (2)
Not assessed/missing	20 (91)	0	20 (41)

ECOG, Eastern Cooperative Oncology Group.

Safety and Tolerability

- Part 1
 - 1 DLT (grade 3 mucositis) was observed at 20 mg; maximum tolerated dose was not reached and the RP2D was established as 13.5 mg once daily, based on safety, PK and PD data, and preliminary signals of clinical benefit
- Parts 1 and 2
 - Median exposure to INCB054828 monotherapy as of the data cutoff was 58.5 days (range, 2–385)
 - The most frequent all-cause, all-grade treatment-emergent adverse events (TEAEs) are presented in Table 2
 - The most frequent grade ≥ 3 TEAEs (≥ 5% of patients) were fatigue (8%), pneumonia (8%), and hyponatremia (6%)
 - Fourteen patients (29%) experienced a serious adverse event (SAE); SAEs occurring in ≥ 2 patients included pneumonia (n = 4) and disease progression (n = 2)
 - Twelve patients experienced a TEAE leading to INCB054828 dose interruption (TEAEs in ≥ 2 patients were fatigue [n = 3] and stomatitis [n = 2]); there were no INCB054828 dose reductions due to TEAEs
 - Three patients permanently discontinued INCB054828 treatment due to TEAEs (pneumonia, cerebrovascular accident, depressed consciousness [each n = 1])
 - Four patients (8.2%) died on study due to a TEAE (disease progression [n = 2], pneumonia [n = 1], intracranial hemorrhage [n = 1])

Table 2. TEAEs Reported in ≥ 20% of Patients in Part 1 or Part 2

TEAEs (MedDRA preferred term)	INCB054828 Monotherapy (part 1) (N = 22) (n %)		INCB054828 Monotherapy (part 2) (N = 27) (n %)		INCB054828 Monotherapy (parts 1 and 2) (N = 49) (n %)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
All TEAEs	21 (95)	11 (50)	23 (85)	10 (37)	44 (90)	21 (43)
Hyperphosphatemia	12 (55)	0	13 (48)	0	25 (51)*	0
Fatigue	10 (45)	2 (9)	11 (41)	2 (7)	21 (43)	4 (8)
Alopecia	7 (32)	0	6 (22)	0	13 (27)	0
Dry mouth	6 (27)	0	6 (22)	0	12 (24)	0
Stomatitis	7 (32)	2 (9)	2 (7)	0	9 (18)	2 (4)
Diarrhea	7 (32)	0	1 (4)	0	8 (16)	0
Weight decreased	6 (27)	0	1 (4)	0	7 (14)	0
Dehydration	5 (23)	0	2 (7)	0	7 (14)	0
Dysgeusia	5 (23)	0	2 (7)	0	7 (14)	0

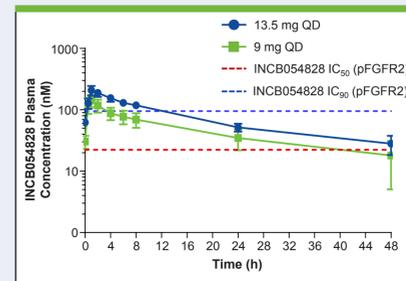
* All events occurred at doses ≥ 6 mg.

MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Pharmacodynamics and Pharmacokinetics of INCB054828

- pFGFR2 was inhibited by 64% and 82% from baseline at steady-state trough INCB054828 levels after 9 and 13.5 mg once daily, respectively
- INCB054828 exhibited low oral clearance and dose-dependent PK (Figure 2); the terminal half-life (15 h) supports once-daily dosing (Figure 2)
- Increase in serum phosphate level correlated with INCB054828 steady-state exposure (Figure 3)

Figure 2. INCB054828 Plasma Concentrations (Mean ± SE) at Steady State Following 9 and 13.5 mg QD Oral Doses of INCB054828



QD, once daily.

Efficacy (Secondary and Exploratory Endpoints)

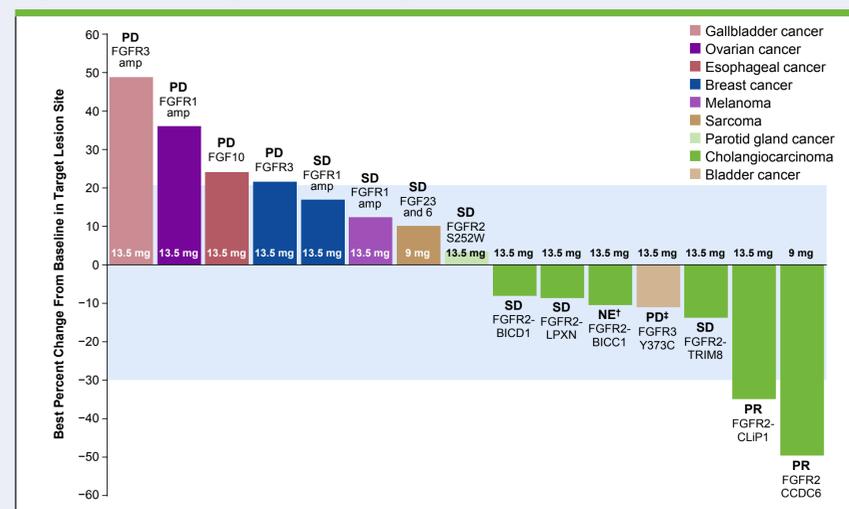
- Best overall response among evaluable patients with FGFR pathway activation in part 2 was 11% (Table 3)
- Best percent change from baseline in target lesion size and best overall response are shown in Figure 4
 - Of 6 patients with cholangiocarcinoma in part 2 who were evaluable for response, 2 had partial responses and 3 had stable disease; all 6 patients had *FGFR2* alterations
- The longest duration of response (225 days [32 weeks]) occurred in a patient with cholangiocarcinoma (*FGFR2-CCDC6* alteration; partial response; 9 mg once daily, ongoing at data cutoff) (Figure 5)

Table 3. Best Overall Response in Efficacy-Evaluable Population (Part 2)

	INCB054828 Monotherapy (n = 27)
Best OR (CR + PR), n (%) [95% CI]	3 (11) [2–29]
CR, n (%)	1 (4)*
PR, n (%)	2 (7)
SD, n (%)	7 (26)
PD, n (%)	5 (19)
Clinical benefit (CR + PR + SD), n (%)	10 (37)
Missing, n (%)	12 (44)
Had not reached the first response assessment at 9 weeks	6 (22)
Discontinued before first response assessment at 9 weeks	4 (15)
No assessment available†	2 (7)

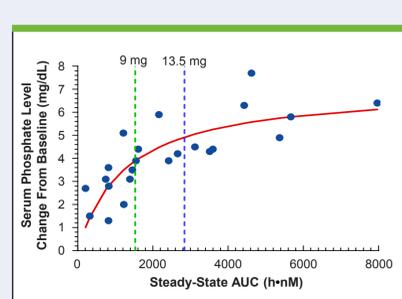
* Based on BM blasts ≤ 5%, resolution of eosinophilia, recovery of blood counts, and elimination of cytogenetic abnormalities. † Response data for 2 patients had not been entered into the database as of the data cutoff date. CR, complete response; OR, overall response; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 4. Best Percent Change From Baseline in Target Lesion Size and Best Overall Response (Part 2)*



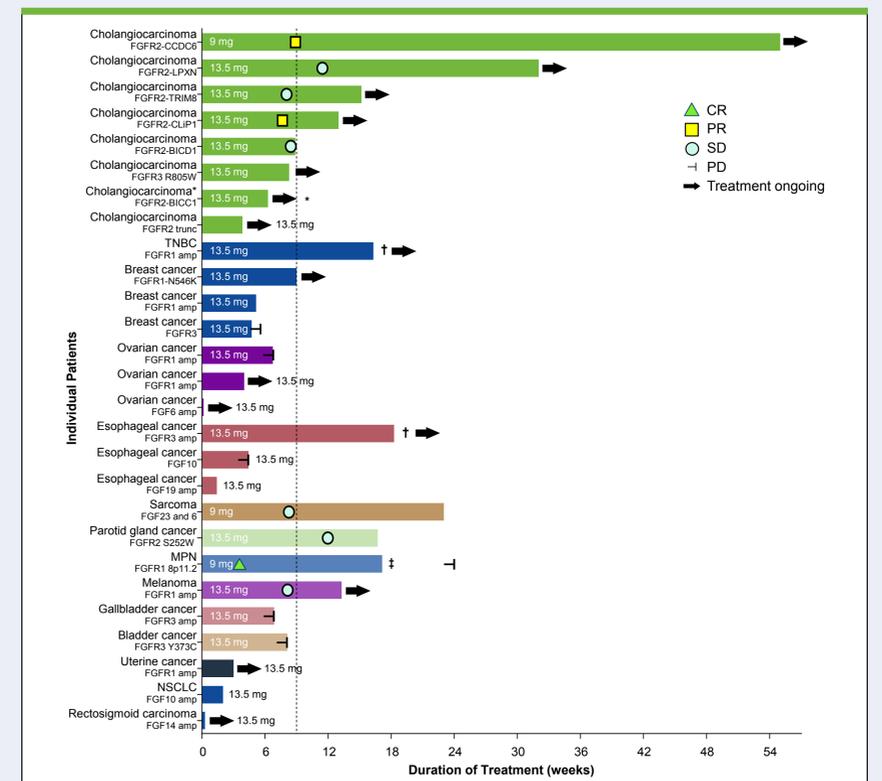
* For patients with data available for best percent change from baseline in target lesion size (n = 15), 1 patient with MPN (FGFR1 8p11.2) had a CR based on BM blasts ≤ 5%, resolution of eosinophilia, recovery of blood counts, and elimination of cytogenetic abnormalities. † 1 patient was not evaluable for response because they had not reached the first response assessment at 9 weeks. ‡ 1 patient had a new lesion. The blue shaded area corresponds to criteria for PR (at least 30% decrease) and PD (at least 20% increase) in the sum of diameters of target lesions. NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 3. Relationship of Serum Phosphate Level and INCB054828 Steady-State Exposure



AUC, area under the curve.

Figure 5. Duration of Treatment and Response (Part 2)



* Tumor type and *FGFR* alteration is shown for each patient. Response assessment was performed on day 14 of every third cycle (± 2 days) or approximately every 9 weeks. Dotted line indicates first on-study assessment. † 1 patient was not evaluable for response because they had not reached the first response assessment at 9 weeks. ‡ Response data not entered into the database as of the data cutoff date. † 1 patient with MPN had a CR based on BM blasts ≤ 5%, resolution of eosinophilia, recovery of blood counts, and elimination of cytogenetic abnormalities. MPN, myeloproliferative neoplasm; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; TNBC, triple-negative breast cancer.

Conclusions

- INCB054828 monotherapy is generally well tolerated at the established RP2D of 13.5 mg once daily
- Hyperphosphatemia was the most common TEAE
- PK/PD data support once-daily dosing and sustained inhibition of FGFR signaling at doses > 9 mg
- Preliminary antitumor activity was observed in tumors with *FGFR2* pathway activation
 - Partial responses occurred in 2 patients with cholangiocarcinoma (*FGFR2* alterations), both of which were ongoing at data cutoff
- Enrollment in parts 2 and 3 is ongoing

Author Disclosures

Saleh: Genentech – PI/Contract Employment, Speaker's Bureau, Honoraria. Gutierrez: BMS – Speaker's Bureau; Merck – Speaker's Bureau. Subbiah: None. Smith: None. Asatiani: Incyte – Employment and Stock Ownership. Lihou: Incyte – Employment and Stock Ownership. Zhen: Incyte – Employment and Stock Ownership. Yeleswaram: Incyte – Employment and Stock Ownership. Ji: Incyte – Employment and Stock Ownership. Nemunaitis: Gradalis – Employment and Stock Ownership; Amgen – Speaker's Bureau; Honoraria; AstraZeneca – Advisory Board Member, Speaker's Bureau, Honoraria.

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