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Interim Results of fight-201, A Phase 2, Open-Label, Multicenter Study of INCB054828 Dosed Intermittently in Patients With Metastatic or Surgically Unresectable Urothelial Carcinoma (UC) Harboring Fibroblast Growth Factor (*FGF*)/*FGF* Receptor (*FGFR*) Genetic Alterations

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Background

- Platinum-based chemotherapy is the treatment of choice for patients with metastatic, inoperable, or recurrent urothelial carcinoma (UC); median overall survival (mOS) with cisplatin-based chemotherapy is approximately 12 to 15 months[1]
  - Patients whose disease progresses on platinum-based chemotherapy or who are ineligible due to inadequate renal function or poor performance status have limited treatment options[1]
- Immune checkpoint inhibitors (ICPIs) have improved outcomes in some patients with platinum-resistant and/or -ineligible metastatic UC; however, benefit may be limited to patients with higher positive tumor and infiltrating immune cell staining for programmed death ligand-1 (PD-L1)[2,3]
- *FGF/FGFR* genetic alterations are implicated in the pathogenesis of UC, most commonly *FGFR3* mutations (≈ 12%) and translocations (≈ 3-6%),[4-6] *FGFR3* genetic alterations are more common in patients with immune desert luminal cluster I subtype UC; these patients are expected to receive less benefit from ICPIs[8-10]
- Pemigatinib (INCB054828) is a selective, potent, oral inhibitor of FGFR1, 2, and 3, and has shown efficacy in tumors with various *FGFR* alterations[11]
- Fibroblast Growth Factor Receptor Inhibitor in Oncology and Hematology Trials (fight)-201 is a phase 2, open-label, multicenter study to evaluate the efficacy and safety of pemigatinib in patients with metastatic or surgically unresectable UC harboring *FGFR3* mutations and translocations (cohort A) and other *FGF/FGFR* genetic alterations (cohort B) (NCT02872714)

Objective

- To evaluate pemigatinib monotherapy in patients with histologically confirmed metastatic or unresectable UC harboring *FGF/FGFR* alterations treated in fight-201

Methods

Key Inclusion Criteria

- Patients aged ≥ 18 years with metastatic or surgically unresectable UC with documented *FGF/FGFR* alterations who failed ≥ 1 previous systemic treatment or who are cisplatin ineligible due to either:
  - Poor performance status (ie, Eastern Cooperative Oncology Group performance status [ECOG PS] of 2), or
  - Insufficient renal function (creatinine clearance < 60 mL/min)
- ECOG PS ≤ 2
- Adequate hepatic function
  - Total bilirubin levels < 1.5 × upper limit of normal (ULN); < 2.5 × ULN for patients with Gilbert syndrome or metastatic disease involving liver
  - Aminotransferase levels ≤ 2.5 × ULN; ≤ 5 × ULN for liver metastases
- Adequate renal function
  - Creatinine clearance > 30 mL/min
- Serum phosphate levels ≤ institutional ULN
- Serum calcium levels within institutional normal range
- Life expectancy ≥ 12 weeks

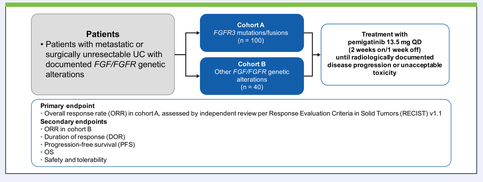
Key Exclusion Criteria

- Treatment with any investigational drugs within 28 days of first dose of pemigatinib treatment; no prior treatment with selective FGFR inhibitors
- History/current evidence of ectopic mineralization/calcification or current evidence of corneal disorder/keratopathy

Study Design

- Patients with *FGFR3* mutations/fusions (cohort A) or other *FGF/FGFR* genetic alterations (cohort B) are enrolled **(Figure 1)**
  - Patients may be screened and enrolled based on local genomic sequencing but all patients must have tumor samples sequenced and confirmed through the sponsor's central laboratory (Foundation Medicine)
  - Sequencing is done using a next-generation sequencing platform on archived samples
- Patients self-administer pemigatinib 13.5 mg orally once daily (QD) on a 21-day cycle (2 weeks on/1 week off) until disease progression or unacceptable toxicity
- Hyperphosphatemia is managed with diet modification, phosphate binders, or dose modification
- Opthalmic exams are done at baseline and during treatment, including optic coherence tomography for patients with suspected serous retinal detachment

Figure 1. Study Design and Endpoints



Statistical Methods

- Efficacy-evaluable patients include all enrolled patients who have *FGF/FGFR* alterations confirmed through the sponsor's central laboratory and receive ≥ 1 dose of study drug
- Safety-evaluable patients include all enrolled patients who receive ≥ 1 dose of study drug
- The primary endpoint, ORR in cohort A, is defined as the proportion of patients with a best response of complete response or partial response (PR) by RECIST v1.1 as assessed by a centralized radiological review committee
  - An ORR of 35% is considered clinically meaningful in this setting, and a sample size of approximately 100 patients is estimated to provide a 95% CI with a lower limit of > 25%
  - The 95% CI for ORR, as assessed by a centralized radiological review committee, is calculated based on exact method for binomial distribution
- DOR, PFS, and OS are analyzed using the Kaplan-Meier method

Results

Patients

- At data cutoff (February 7, 2018), 108 patients were enrolled. This poster presents data from an additional 5 months of followup from these patients (July 6, 2018) **(Table 1)**
  - The efficacy-evaluable population consisted of 103 patients, and the safety-evaluable population consisted of 108 patients (5 patients did not have *FGF/FGFR* alterations confirmed through the sponsor's central laboratory)
    - Among 103 patients, 61 were enrolled in cohort A and 42 in cohort B
    - Of 61 patients in cohort A, 49 discontinued treatment and 12 had treatment ongoing
- Baseline demographics and disease characteristics are shown in **Table 2**. For cohort A:
  - Median age was 66 (range, 44-88) years, and the majority of patients were male (75%)
  - 38% received ≥ 3 prior therapies
  - The majority (82%) of patients had ECOG PS ≤ 1
  - 90% of patients received prior platinum-based chemotherapy
  - 38% of patients received a prior programmed death 1 (PD-1)/PD-L1 inhibitor
  - 74% had prior surgery
  - The majority (69%) of patients' primary cancer was in the bladder; 15% and 13% of primary cancers were in the ureter and renal pelvis, respectively (1 additional patient had primary cancer in both ureter and renal pelvis, data were missing for 1 patient)
  - The majority of patients (66%) had visceral metastases (defined as liver and/or lung metastases)
- Median number of pemigatinib treatment cycles in cohort A was 6 (range, 1-15); median exposure was 17 (range, 0.7 - 47.4) weeks

Table 1. Patient Disposition

Variable, n (%)	Cohort A (n = 61)	Cohort B (n = 42)
Patients treated	61 (100)	42 (100)
Treatment ongoing	12 (19.7)	6 (14.3)
Treatment discontinued	49 (80.3)	36 (85.7)
Reason for discontinuation		
PD	38 (62.3)	26 (61.9)
AE	3 (7.1)	3 (7.1)
Physician decision	3 (4.9)	1 (2.4)
Death	4 (6.6)	0 (0)
Withdrawal by patient	2 (3.3)	2 (4.8)
Other	1 (1.6)	4 (9.5)

AE, adverse event; PD, progressive disease.

Table 2. Baseline Demographics and Disease Characteristics

	Cohort A (n = 61)	Cohort B (n = 42)
Age, median (range), years	66 (44-88)	65 (38-84)
Sex, n (%)		
Men	46 (75.4)	30 (71.4)
Women	15 (24.6)	12 (28.6)
Race, n (%)		
White	37 (60.7)	29 (69.0)
Black/African American	0 (0)	0 (0)
Asian	0 (0)	1 (2.4)
Other	20 (32.8)	12 (28.6)
Missing	4 (6.6)	0 (0)
ECOG PS, n (%)		
0	22 (36.1)	19 (45.2)
1	28 (45.9)	18 (42.9)
2	11 (18.0)	5 (11.9)
Prior therapy, n (%)		
0	3 (4.9)	0 (0)
1	12 (19.7)	15 (35.7)
2	23 (37.7)	15 (35.7)
≥ 3	23 (37.7)	12 (28.6)
Type of prior therapy, n (%)		
Platinum chemotherapy	55 (90.2)	40 (95.2)
PD-1/L1 inhibitor	23 (37.7)	17 (40.5)
Prior surgery, n (%)		
Yes	45 (73.8)	38 (90.5)
No	16 (26.2)	4 (9.5)
Prior radiation, n (%)		
Yes	19 (31.1)	16 (38.1)
No	42 (68.9)	26 (61.9)
Primary tumor location, n (%)		
Bladder	42 (68.9)	32 (76.2)
Renal pelvis	8 (13.1)	5 (11.9)
Ureter	9 (14.8)	3 (7.1)
Renal pelvis, ureter	1 (1.6)	1 (2.4)
Missing	1 (1.6)	1 (2.4)
Visceral metastases, n (%)		
Present	40 (65.6)	30 (71.4)
Absent	21 (34.4)	12 (28.6)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-1, programmed death-1; PD-L1, programmed death ligand-1.

Efficacy

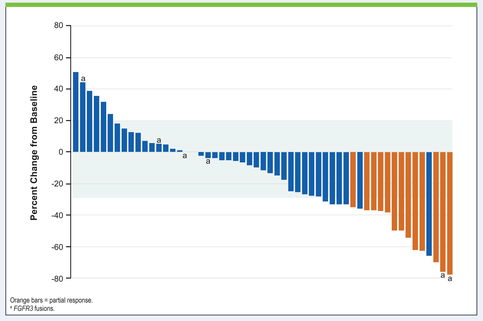
- Primary endpoint: The ORR in cohort A was 21% (95% CI, 12%-34%) **(Table 3; Figures 2 and 4)** and included 13 confirmed PRs. 22 patients had stable disease (SD)
- In cohort B, 1 patient with *FGF10* amplification had a confirmed PR **(Figures 3 and 5)**
- Median DOR in cohort A was 6 months, and median PFS was 4 months (95% CI, 3.0-5.6 months)

Table 3. ORR by Patient Cohort (Assessed by Independent Reviewer)

Variable	Cohort A (n = 61)	Cohort B (n = 42)
ORR, n (%)	13 (21.3)	1 (2.4)
[95% CI]	[11.9-33.7]	[0.0-12.6]
PR (confirmed)	13	1
SD	22 (36.1)	10 (23.8)
PD	20 (32.8)	25 (59.5)
NE	3[a] (4.9)	3 (7.1)
Missing	3[b] (4.9)	3 (7.1)
Median DOR (95% CI), months	6.2 (4.2-8.4)	NE
Median PFS (95% CI), months	4.1 (3.0-5.6)	2.0 (1.9-2.1)

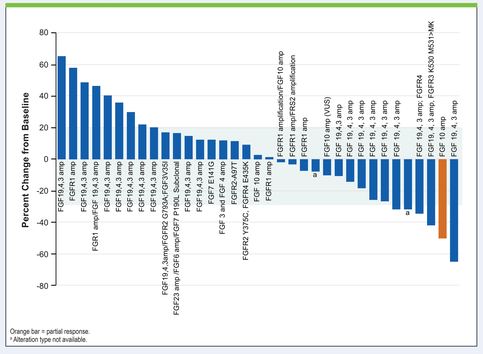
CI, confidence interval; DOR, duration of response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
[a] 3 patients had SD earlier than 49 days.
[b] 1 patient was not assessed by central reviewer prior to data cut; 2 patients died before the first post-baseline assessment.

Figure 2. Best Percent Change From Baseline in Target Lesion Size in Patients With UC and *FGFR3* Mutations/Fusions (Cohort A)



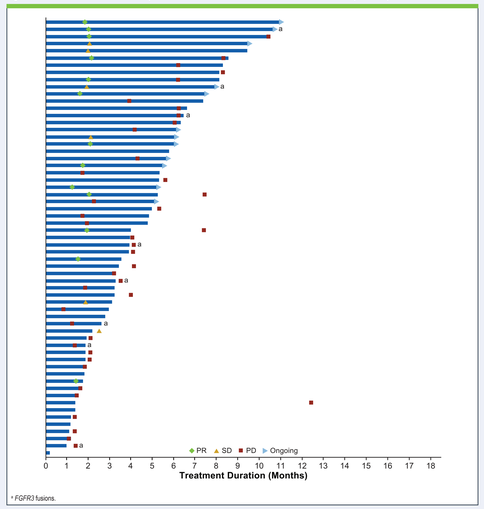
Orange bars = partial response.
[a] *FGFR3* fusions.

Figure 3. Best Percent Change From Baseline in Target Lesion Size in Patients With UC and Other *FGF/FGFR* Alterations (Cohort B)



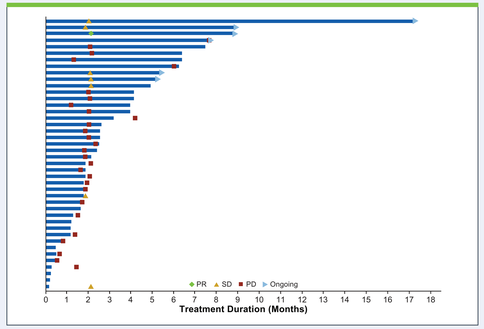
Orange bar = partial response.
[a] Alteration type not available.

Figure 4. Duration of Treatment and Response in Patients With UC and *FGFR3* Mutations/Fusions (Cohort A)



[a] *FGFR3* fusions.

Figure 5. Duration of Treatment and Response in Patients with UC and Other *FGF/FGFR* Alterations (Cohort B)



Safety and Tolerability

- Pemigatinib was generally safe and well tolerated
  - Treatment-related AEs (TRAEs) occurred in 93% of safety-evaluable patients **(Table 4)**
  - Pemigatinib dose was reduced due to treatment-emergent AEs (TEAEs) in 16% and 12% of patients in cohorts A and B, respectively; few patients discontinued due to TEAEs in each cohort (5% vs 7%, respectively); TEAEs that led to discontinuation were serous retinal detachment, diarrhea, general physical health deterioration, increased blood creatinine, syncope, and acute kidney injury (n=1 each)
  - 8% and 7% of patients in cohorts A and B, respectively experienced serious TRAEs including pericardial effusion, serous retinal detachment, nausea, fatigue, malaise, increased blood creatinine, syncope, dyspnea, and phlebitis (n=1 each)
  - 10 fatal TEAEs were reported; none was deemed related to study treatment
- The most common TEAEs across cohorts included diarrhea (44%), alopecia (40%), constipation (35%), and stomatitis (34%); a full list of the most common TEAEs is provided in **Table 5**
- Grade ≥ 3 TEAEs that occurred in > 5% of patients were anemia, urinary tract infections, stomatitis (7% each), and fatigue, general physical health deterioration, and hyponatremia (6% each)

Table 4. Safety Overview

Events, n (%)	Total (N = 108)
Any TEAE	107 (99.1)
Any TRAE	100 (92.6)
Any serious TEAE	54 (50.0)
Discontinuation due to TEAE	6 (5.6)
Treatment interruption due to TEAE	40 (37.0)
Dose reduction due to TEAE	15 (13.9)
Any fatal TEAE	10 (9.3)

TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Table 5. Most Common TEAEs[a] That Occurred in ≥ 20% of Patients

	Total (N = 108)	
Events, n (%)	All Grades	Grade ≥ 3
Diarrhea	47 (43.5)	3 (2.8)
Alopecia	43 (39.8)	1 (0.9)
Constipation	38 (35.2)	1 (0.9)
Stomatitis	37 (34.3)	8 (7.4)
Fatigue	35 (32.4)	6 (5.6)
Dry mouth	35 (32.4)	1 (0.9)
Hyperphosphatemia[b]	34 (31.5)	1 (0.9)
Decreased appetite	32 (29.6)	4 (3.7)
Dysgeusia	32 (29.6)	0 (0)
Nausea	28 (25.9)	1 (0.9)
Asthenia	27 (25.0)	4 (3.7)
Abdominal pain	25 (23.1)	3 (2.8)
Back pain	22 (20.4)	4 (3.7)

TEAE, treatment-emergent adverse event.
[a] Patients were counted once under each Medical Dictionary for Regulatory Activities preferred term.
[b] Hyperphosphatemia was managed with phosphate binders, diet, and/or dose interruption.

Conclusions

- **Pemigatinib was generally well tolerated and showed preliminary efficacy in previously treated patients with UC harboring *FGFR3* mutations/fusions**
  - **The ORR was 21% (95% CI, 12%-34%)**
  - **Median PFS was 4 months (95% CI, 3.0-5.6 months)**
  - **Most common TEAEs included diarrhea, alopecia, constipation, and stomatitis**
- **Preliminary results from this study demonstrate that patients with UC harboring *FGFR3* mutations/ fusions may benefit from targeted therapy with pemigatinib. More intensive treatment regimen may increase efficacy**
- **The protocol has been amended to enroll patients with *FGFR3* mutations/fusions on a continuous dosing schedule, with the starting dose of 13.5 mg**

Disclosures

Necchi: Incyte, Roche, Merck, AstraZeneca, Clovis Oncology, BioClin Therapeutics, Janssen, Bayer. **Pouessel:** Janssen, Astellas, Sanofi, AstraZeneca, Pfizer, Novartis. **Leibowitz-Amit:** Janssen, Bayer, Roche, Bristol-Myers Squibb, MSD; Pfizer Advisory Committee Member. **Flechon:** Pfizer, Novartis, Ipsen, Astellas, Sanofi, Janssen, Roche, MDS, Bristol-Myers Squibb. **Gupta:** Pfizer, Five Prime Therapeutics, Hoosier Oncology Group, Rexahn Pharmaceuticals, Incyte, Bristol-Myers Squibb, Novartis, LSK BioPharma, Mirati Therapeutics, Merck. **Barthelemy:** Bristol-Myers Squibb, Novartis, Pfizer, Roche, MDS, Janssen Cilag, Sanofi, Astellas. **Maio:** Bristol-Myers Squibb, GlaxoSmithKline, AstraZeneca, Roche, MDS, Incyte; member of Bristol-Myers Squibb, GlaxoSmithKline, AstraZeneca, Roche, MSD, and Incyte advisory committees. **Zhu:** Sanofi. **Asatiani:** Incyte – employment and stock ownership. **Lihou:** Incyte – employment and stock ownership. **Zhen:** Incyte – employment and stock ownership. **Loriot:** Seattle Genetics, Astellas, Roche, AstraZeneca, MDS, Bristol-Myers Squibb, Sanofi, Janssen, Pfizer.

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References

1. Seront E, Machiels JP. *Cancer Treat Rev*. 2015;41:341-353.
2. Bellmunt J, et al. *N Engl J Med*. 2017;376:1015-1026.
3. US Food and Drug Administration. https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm608253.htm. Accessed October 1, 2018.
4. Turner N, Grose R. *Nat Rev Cancer*. 2010;10:116-129.
5. Weiss J, et al. *Sci Transl Med*. 2010;2:62ra93.
6. Heist RS, et al. *J Thorac Oncol*. 2012;7:1775-1780.
7. Lombardi B, et al. *Oncotarget*. 2017;8:102898-102911.
8. Cancer Genome Atlas Research Network. *Nature*. 2014;507:315-322.
9. Damrauer JM, et al. *Proc Natl Acad Sci U S A*. 2014;111:3110-3115.
10. Le Goux C, et al. *Urol Oncol*. 2017;35:257-263.
11. Liu PCC, et al. AACR 2015. Abstract 771.

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