MPN-384

A Phase 2 Study of Pemigatinib (FIGHT-203; INCB054828) in Patients With Myeloid/Lymphoid Neoplasms With Fibroblast Growth Factor Receptor 1 Gene Rearrangement

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Alessandro M. Vannucchi,[1] **Jay L. Patel**,[2] **William E. Shomali**,[3] **Tracy I. George**,[2] **Andreas Reiter**,[4] **Alessandro Rambaldi**,[5] **Stephen Oh**,[6] **Kensuke Usuki**,[7] **Claire N. Harrison**,[8] **Maria Luisa Veronese**,[9] **Aidan Gilmartin**,[10] **Huiling Zhen**,[10] **Srdan Verstovsek**,[11] **Natalia Oliveira**,[9] **Jason Gotlib**,[3] **Jean-Jacques Kiladjian**[12]

[1]University of Florence, CRIMM, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy; [2]ARUP Laboratories and University of Utah School of Medicine, Salt Lake City, UT, USA; [3]Division of Hematology, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA, USA; [4]University Hospital Mannheim, Heidelberg University, Mannheim, Germany; [5]Department of Oncology and Hematology, University of Milan and Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy; [6]Washington University School of Medicine, St. Louis, MO, USA; [7]Department of Hematology, NTT Medical Center Tokyo, Tokyo, Japan; [8]Guy's and St Thomas' NHS Foundation Trust, Guy's Hospital, London, UK; [9]Incyte International Biosciences Sàrl, Morges, Switzerland; [10]Incyte Corporation, Wilmington, DE, USA; [11]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [12]Hôpital Saint-Louis, Paris, France

Introduction

- Myeloid/lymphoid neoplasms with fibroblast growth factor receptor 1 (*FGFR1*) gene rearrangement (MLN*FGFR1*) are rare, aggressive hematologic malignancies that belong to the World Health Organization category "MLN with eosinophilia and tyrosine kinase gene fusions"[1,2]
- In patients with MLN*FGFR1*, the presence of t(8;13)(p11;q12), t(8;22)(p11;q11), or another chromosome band 8p11 reciprocal translocation is a key diagnostic feature that results in *FGFR1* fusion genes and constitutive FGFR1 activation[2]
- Currently, there are 16 known FGFR1 fusion partners, among which, *ZMYM2* (13q12) and *BCR* (22q11) are the most common[3-5]
- Pemigatinib is a potent oral FGFR1-3 inhibitor approved by the US Food and Drug Administration in August 2022 for the treatment of adults with relapsed or refractory MLN*FGFR1*, based on pivotal results of the FIGHT-203 study (NCT03011372)[7]

Objective

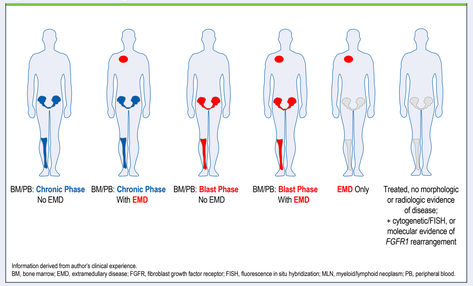
- To present updated data from the FIGHT-203 study, including clinical, cytogenetic, and molecular responses

Methods

Study Design

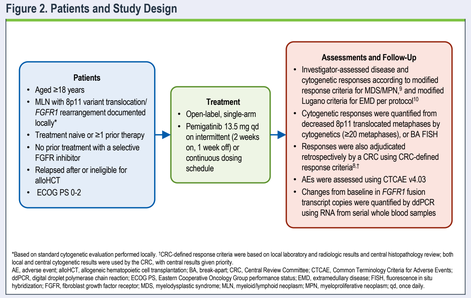
- FIGHT-203 is a phase 2, open-label, multicenter study evaluating the efficacy and safety of pemigatinib in adults with MLN*FGFR1*
- Disease presentation of patients with MLN*FGFR1* was categorized as outlined in **Figure 1**
- Key eligibility criteria are outlined in **Figure 2**
- Patients received oral pemigatinib 13.5 mg once daily (intermittent dose [2 weeks on/1 week off] or continuous dose)

Figure 1. MLN*FGFR1*: Categories of Presentation[8]



Information derived from author's clinical experience.
BM, bone marrow; EMD, extramedullary disease; FGFR, fibroblast growth factor receptor; FISH, fluorescence in situ hybridization; MLN, myeloid/lymphoid neoplasm; PB, peripheral blood.

Figure 2. Patients and Study Design



*Based on standard cytogenetic evaluation performed locally. †CRC-defined response criteria were based on local laboratory and radiologic results and central histopathology review; both local and central cytogenetic results were used by the CRC, with central results given priority.
AE, adverse event; alloHCT, allogeneic hematopoietic cell transplantation; BA, break-apart; CRC, Central Review Committee; CTCAE, Common Terminology Criteria for Adverse Events; ddPCR, digital droplet polymerase chain reaction; ECOG PS, Eastern Cooperative Oncology Group performance status; EMD, extramedullary disease; FISH, fluorescence in situ hybridization; FGFR, fibroblast growth factor receptor; MDS, myelodysplastic syndrome; MLN, myeloid/lymphoid neoplasm; MPN, myeloproliferative neoplasm; qd, once daily.

Methods (cont'd)

Endpoints

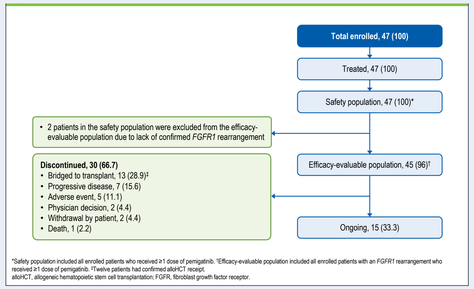
- The primary endpoint was percentage of complete responses (CRs) as best overall response, as assessed by investigator and adjudicated retrospectively by a CRC
- Secondary endpoints were overall response rate, complete cytogenetic response rate (CCyR), partial cytogenetic response rate, duration of CR (DOCR), duration of overall response (DOR), progression-free survival (PFS), overall survival (OS), and safety
- As an exploratory analysis, *FGFR1* fusion partner genes were identified with anchored multiplex polymerase chain reaction (PCR)-based next-generation sequencing (Integrated DNA Technologies, Inc. Coralville, IA, USA) of RNA extracted from peripheral blood
- Changes from baseline in specific FGFR1 fusion RNA transcript copies were quantified with droplet digital PCR of serial whole blood samples collected on day (D) 1 and D15 of cycle (C) 1, D1 of C2, C4, and C8; then D1 of every 4 cycles (estimated limit of detection, 0.05 copies/µL)

Results

Patient Disposition

- As of July 17, 2023, 47 patients were enrolled (**Figure 3**)
  - 45 patients were analyzed for efficacy
- Treatment was ongoing in 15 patients, and 30 patients had discontinued
  - The most common reasons for discontinuation were bridging to allogeneic hematopoietic stem cell transplantation (alloHCT) (28.9%) and progressive disease (15.6%)
  - Of the 13 patients who bridged to alloHCT; 9 out of 9 patients who had response data available were in complete remission at the time of initial alloHCT

Figure 3. Patient Disposition, n (%)



*Safety population included all enrolled patients who received ≥1 dose of pemigatinib. †Efficacy-evaluable population included all enrolled patients with an *FGFR1* rearrangement who received ≥1 dose of pemigatinib. ‡Twelve patients had confirmed alloHCT receipt.
alloHCT, allogeneic hematopoietic stem cell transplantation; FGFR, fibroblast growth factor receptor.

Baseline Characteristics

- Among 45 patients with MLN*FGFR1*, 40 had received ≥1 prior therapy and 3 had received prior alloHCT (**Table 1**)
  - 12 patients had peripheral blood eosinophilia at baseline
- Median follow-up was 47.4 (range, 13.7-74.7) months; median duration of treatment was 9.0 (range, 1.2-74.8)

Table 1. Baseline Characteristics of Patients With MLN*FGFR1*

Characteristic	Safety Population (N=47)	Efficacy-Evaluable Population (N=45)
Age, median (range), years	62.0 (23-78)	61.0 (23-78)
Female, n (%)	25 (53.2)	25 (55.6)
Race, n (%)		
White	30 (63.8)	28 (62.2)
Black or African American	4 (8.5)	4 (8.9)
Other*	8 (17.0)	8 (17.8)
ECOG PS, n (%)		
0-1	41 (87.2)	39 (86.7)
≥2	6 (12.8)	6 (13.3)
No. of patients with ≥1 prior therapy for MLN*FGFR1*, n (%)	41 (87.2)†	40 (88.9)‡
Prior alloHCT, n (%)	3 (6.4)	3 (6.7)
Peripheral blood eosinophilia (>0.5×10⁹/L) at baseline (per CRC), n (%)	12 (25.5)	12 (26.7)

*Other includes Asian and other. †One prior therapy (n=24), 2 prior therapies (n=8), 3 prior therapies (n=4), 4 prior therapies (n=1), >4 prior therapies (n=4). ‡One prior therapy (n=23), 2 prior therapies (n=8), 3 prior therapies (n=4), 4 prior therapies (n=1), >4 prior therapies (n=4).
alloHCT, allogeneic hematopoietic stem cell transplantation; CRC, Central Review Committee; ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; MLN, myeloid/lymphoid neoplasm.

Disease Presentation

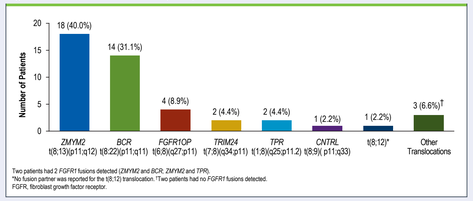
- At baseline, most patients had myeloid bone marrow involvement (75.6%) (**Table 2**)
  - 53.3% of patients had chronic-phase (CP) disease only, without extramedullary disease
- The most common *FGFR1* fusion gene partners were *ZMYM2* (40.0%) and *BCR* (31.1%) (**Figure 4**)

Table 2. Disease Presentation at Baseline

Disease Presentation, n (%)	Safety Population (N=47)	Efficacy-Evaluable Population (n=45)*
BM involvement by lineage (per CRC)		
No morphologic evidence of disease	7 (14.9)*	7 (15.6)†
Myeloid neoplasm	35 (74.5)	34 (75.6)
Lymphoid neoplasm	2 (4.3)	2 (4.4)
Mixed-phenotype neoplasm	3 (6.4)	3 (6.7)
Presentation category (BM and/or EMD involvement; per CRC)		
CP only (no EMD)	24 (51.1)	24 (53.3)
BP disease (EMD represents a BP component)	19 (40.4)	18 (40.0)
CP with EMD	4 (8.5)	4 (8.9)
BP without EMD	7 (14.9)	6 (13.3)
BP with EMD	4 (8.5)	4 (8.9)
EMD only	4 (8.5)	4 (8.9)
Treated MLN without morphologic evidence of BM or EMD involvement (persistent 8p11 translocation and/or *FGFR1* rearrangement)	3 (6.4)	3 (6.7)

*The efficacy evaluable population excluded 2 patients who did not have a confirmed FGFR1 rearrangement: one of these patients had a baseline presentation of BP without EMD and the other had missing disease presentation data at baseline. †Three patients had treated MLN without BM/PB/EMD involvement but persistent 8p11 translocation and/or FGFR rearrangement; 3 patients had myeloid sarcoma EMD; and 1 patient had T-lymphoblastic leukemia/lymphoma EMD.
BM, bone marrow; BP, blast phase; CP, chronic phase; CRC, Central Review Committee; EMD, extramedullary disease; FGFR, fibroblast growth factor receptor; MLN, myeloid/lymphoid neoplasm.

Figure 4. *FGFR1* Fusion Partners (n=45)



Two patients had 2 *FGFR1* fusions detected (*ZMYM2* and *BCR*; *ZMYM2* and *TPR*).
*No fusion partner was reported for the t(8;12) translocation. †Two patients had no *FGFR1* fusions detected.
FGFR, fibroblast growth factor receptor.

Response

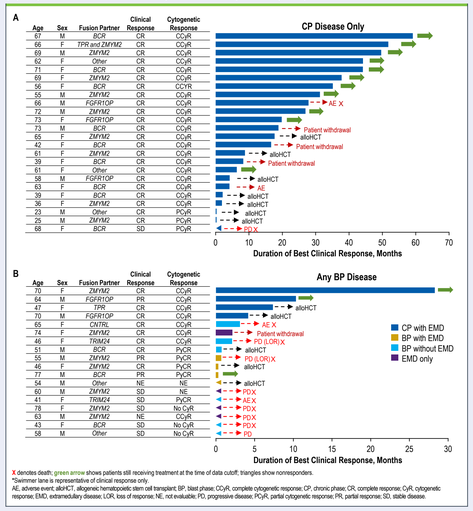
- In efficacy-evaluable patients, CR rate and CCyR rates were 73.8% (CP, 95.8%; any blast phase [BP], 44.4%) and 71.1% (CP, 87.5%; any BP, 44.4%), respectively (**Table 3, Figure 5**)
- Among patients with ≥1 and without prior treatment, CR rates were 70.0% and 80.0%, respectively
- Median DOCR was not reached (NR; range, 27.9-NR) months
  - 85.8% of patients were estimated to have maintained a CR at 24 months
- Median PFS and OS was not reached at data cutoff; the estimated PFS and OS at 24 months were 73.0% and 76.4%, respectively

Table 3. Response

Response	Investigator (N=45)	CRC (N=45)
	n=45	n=42*
CR rate, n (%) [95% CI]	31 (68.9) [53.4-81.8]	31 (73.8) [58.0-86.1]
CP only (n=24)	22 (91.7) [73.0-99.0]	23 (95.8) [78.9-99.9]
Any BP (n=18)	6 (33.3) [13.3-59.0]	8 (44.4) [21.5-69.2]
1 prior therapy (n=23)	17 (73.9) [51.6-89.8]	18 (78.3) [56.3-92.5]
>1 prior therapy (n=17)	10 (58.8) [32.9-81.6]	10 (58.8) [32.9-81.6]
No prior therapy (n=5)	4 (80.0) [28.4-99.5]	4 (80.0) [28.4-99.5]
ORR, n (%) [95% CI]	35 (77.8) [62.9-88.8]	34 (81.0) [65.9-91.4]
Best overall response, n (%)	n=45	n=42*
CR	31 (68.9)	31 (73.8)
PR	4 (8.9)	3 (7.1)
SD	9 (20.0)	6 (14.3)
PD	1 (2.2)	1 (2.4)†
NE/missing	0	1 (2.4)†
Time to CR, median (95% CI), months	3.4 (1.3-45.5)	1.5 (1.3-9.7)
Duration of CR, median (95% CI), months	NE (25.5-NE)	NR (27.9-NR)
CCyR rate, n (%) [95% CI]	32 (71.1) [55.7-83.6]	32 (71.1) [55.7-83.6]
CP only (n=24)	20 (83.3) [62.6-95.3]	21 (87.5) [67.6-97.3]
Any BP (n=18)	9 (50.0) [26.0-74.0]	8 (44.4) [21.5-69.2]

*Three patients were assessed only for cytogenetic responses, because they had no morphologic evidence of disease. †One patient was NE for response before having PD.
‡One patient was NE for response because no data were available for review.
BP, blast phase; CCyR, complete cytogenetic response; CI, confidence interval; CP, chronic phase; CR, complete response; CRC, Central Review Committee; NE, not evaluable; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 5. (A) Best Clinical and Cytogenetic Response in Patients With CP Only or (B) Any BP Disease in the Efficacy-Evaluable Population (n=45)



X denotes death; green arrow shows patients still receiving treatment at the time of data cutoff; triangles show nonresponders.
*Swimmer lane is representative of clinical response only.
AE, adverse event; alloHCT, allogeneic hematopoietic stem cell transplant; BP, blast phase; CCyR, complete cytogenetic response; CP, chronic phase; CR, complete response; CyR, cytogenetic response; EMD, extramedullary disease; LOR, loss of response; NE, not evaluable; PD, progressive disease; PCyR, partial cytogenetic response; PR, partial response; SD, stable disease.

Safety

- Of the 47 patients evaluated for safety, all patients had a treatment-emergent adverse event (TEAE) and 39 had grade ≥3 TEAEs
- Most common TEAEs were hyperphosphatemia (76.6%), diarrhea (61.7%), and alopecia (57.4%) (**Table 4**)
  - Most common grade ≥3 TEAEs were stomatitis (19.1%) and anemia (14.9%)
- Treatment-related AEs were reported in 46 patients
  - 30 patients had grade ≥3 treatment-related AEs; the most common was stomatitis (14.9%)
- Serious TEAEs were reported in 27 patients (57.4%)
  - The most common serious TEAEs were acute kidney injury (n=3) and urinary tract infection and atrioventricular block complete (each n=2)
- TEAEs led to pemigatinib dose interruptions and reductions in 63.8% and 59.6% of patients, respectively
  - 10.6% of patients discontinued pemigatinib treatment due to TEAEs
- 4 patients were reported to have fatal TEAEs (acute kidney injury, intervertebral discitis, multiple organ dysfunction syndrome, and malignant neoplasm progression [each n=1]); none were considered related to pemigatinib
- The TEAE profile was similar for intermittent and continuous dosing schedules

Table 4. Most Common TEAEs*

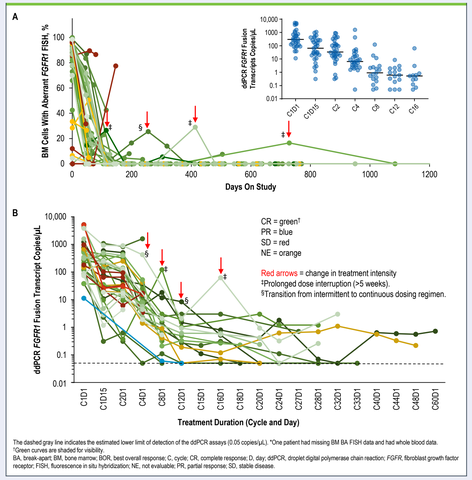
TEAE, n (%)	Patients (N=47)	
	All Grades	Grade ≥3
Hyperphosphatemia†	36 (76.6)	2 (4.3)
Diarrhea	29 (61.7)	1 (2.1)
Alopecia	27 (57.4)	1 (2.1)
Stomatitis	21 (44.7)	9 (19.1)
Dry eye	20 (42.6)	2 (4.3)
Constipation	19 (40.4)	1 (2.1)
Dry mouth	19 (40.4)	0
Nausea	17 (36.2)	0
Decreased appetite	16 (34.0)	2 (4.3)
Abdominal pain	15 (31.9)	1 (2.1)
Anemia	15 (31.9)	7 (14.9)
Epistaxis	14 (29.8)	0
Pain in extremity	13 (27.7)	4 (8.5)
Dry skin	12 (25.5)	1 (2.1)
Rash	12 (25.5)	1 (2.1)

*Occurring in >25% of patients in the safety population. †Hyperphosphatemia includes MedDRA preferred terms of blood phosphorus increased and hyperphosphatemia.
MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Molecular Response

- *FGFR1* fusion transcript copy numbers in serial whole blood decreased during treatment in 30/33 patients with ≥3 measures of fusion frequency increased following dose interruption (>5 weeks), and decreased upon reinitiation of pemigatinib (**Figure 6A**)
- These dynamic changes were consistent with changes in the bone marrow by break-apart fluorescence in situ hybridization (Pearson coefficient = 0.80), including improved responses in patients who transitioned from intermittent dosing to continuous dosing (**Figure 6B**)
- Changes in *FGFR1* fusion transcript copy numbers also reflected changes in treatment intensity; deeper decreases were observed with both methods following the transition from intermittent to continuous dosing
- Among patients with CR, 75.0% (18/24) had >2-log, and 45.8% (11/24) had >3-log reductions in *FGFR1* fusion RNA transcript copy numbers; smaller reductions were observed in patients with stable disease (>2-log reduction, 40% [2/5])

Figure 6. (A) Central *FGFR1* FISH Analysis of BM Cells From Individual Patients (n=44)*; (B) ddPCR Analysis of *FGFR1* Fusion Transcripts From Individual Patients (n=33)



The dashed gray line indicates the estimated lower limit of detection of the ddPCR assays (0.05 copies/µL). *One patient had missing BM BA FISH data and had whole blood data.
†Green curves are shaded for visibility.
BA, break-apart; BM, bone marrow; BOR, best overall response; C, cycle; CR, complete response; D, day; ddPCR, droplet digital polymerase chain reaction; *FGFR*, fibroblast growth factor receptor; FISH, fluorescence in situ hybridization; NE, not evaluable; PR, partial response; SD, stable disease.

Conclusions

- **Pemigatinib is the first treatment to show deep and durable clinical, cytogenetic, and molecular responses in patients with MLN*FGFR1*, regardless of disease presentation and number of prior therapies**
- **Observed toxicities were manageable with dose modification and consistent with the known safety profile of pemigatinib**
- **The results suggest that pemigatinib may offer a long-term treatment option for patients with MLN*FGFR1* ineligible for alloSCT, or may facilitate bridging to alloSCT in eligible patients**

References

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Disclosures

Vannucchi: Honoraria and member of an entity's Board of Directors or advisory boards – *Bristol Myers Squibb, Incyte Corporation, Novartis*; Member of an entity's Board of Directors or advisory boards – *AbbVie*.

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