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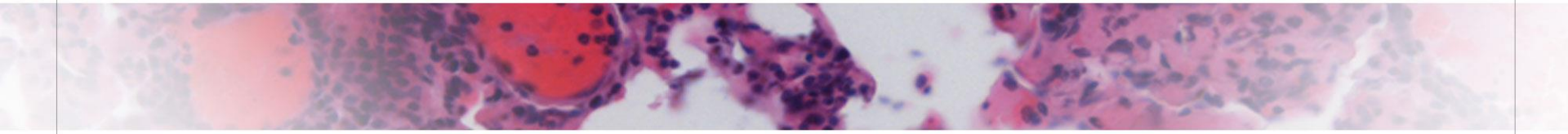


Interim Results From fight-203, a Phase 2, Open-Label, Multicenter Study Evaluating the Efficacy and Safety of Pemigatinib (INCB054828) in Patients With Myeloid/Lymphoid Neoplasms With Rearrangement of *FGFR1*

Srdan Verstovsek[1], Alessandro Vannucchi[2], Alessandro Rambaldi[3], Jason Gotlib[4], Adam Mead[5], Andreas Hochhaus[6], Jean-Jacques Kiladjian[7], Juan Carlos Hernandez-Boluda[8], Ekaterine Asatiani[9], Huiling Zhen[9], Andreas Reiter[10]

[1]The University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [2]Azienda Ospedaliero Universitaria Careggi, Firenze, Italy; [3] Department of Oncology and Hematology, University of Milan and Azienda Socio Sanitaria Territoriale, Papa Giovanni XXIII, Bergamo, Italy; [4]Stanford Cancer Institute, Stanford, CA, USA; [5]Oxford University Hospitals NHS Trust - Churchill Hospital, Oxford, UK; [6]Universitätsklinikum Jena, Jena, Germany; [7]Hôpital Saint-Louis, Paris, France; [8]Hospital Clinico Universitario, Valencia, Spain; [9]Incyte Corporation, Wilmington, DE, USA; [10]Medizinische Fakultät Mannheim der Universität Heidelberg, Mannheim, Germany

Myeloid/lymphoid Neoplasm (MLN) With *FGFR1* Rearrangement

- Rare but aggressive neoplasm characterized by heterogenous presentation[1,2]:
  - Peripheral blood eosinophilia
  - Extramedullary involvement with T-lymphoblastic lymphoma (TLL)
  - Rapid progression to blast phase

Common Fusion Partner[4.5]	Karyotype	Usual Clinical Phenotype
ZMYM2	t(8;13)(p11;q12)	MPN with TLL-like
BCR	t(8;22)(p11;q11)	CML-like

- Molecular pathogenesis results from a chromosomal translocation between *FGFR1* gene, located at the 8p11 locus, and several partner genes[3-6]
- Incidence, best treatment, and response criteria have not been established
  - Highly refractory to chemotherapy[7]
  - Allogeneic HSCT is the only potentially curative option[6-8]

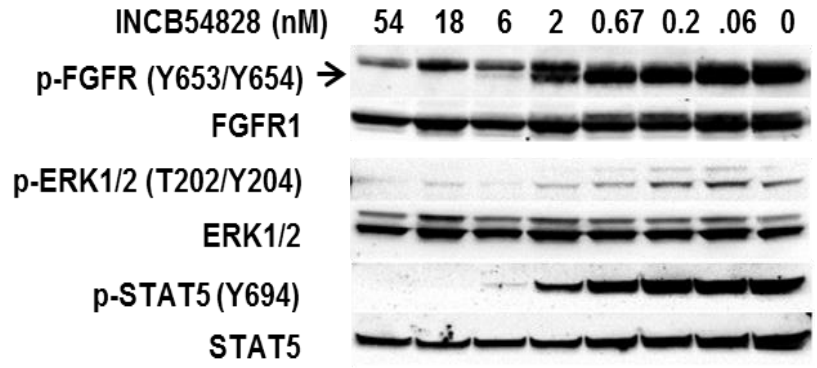
FGFR, fibroblast growth factor receptor; HSCT, allogenic hematopoietic stem cell transplant; MPN, myeloproliferative neoplasm; CML, chronic myeloid leukemia.

1. Strati P, et al., *Leuk Lymphoma*. 2018;59:1672-1676. 2. WHO classification of tumours of haematopoietic and lymphoid tissues. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, and Thiele J, eds. 4th ed. International Agency for Research on Cancer, France; 2016. 3. Macdonald D, et al. *Leukemia.* 1995;9:1628–1630. 4. http://atlasgeneticsoncology.org/Anomalies/8p11inMPDID1091.html. 5. Savage N, et al. J. *Int J Lab Hematol.* 2013;35:491–500. 6. Demiroglu A, et al., *Blood.* 2001;98:3778–3783. 7. Khodadoust MS, et al. *Leukemia.* 2016;30:947–950. 8. Kreil S, et al. *Blood.* 2015; 126(23). Abstract 2812.

Pemigatinib in Patients With MLN Harboring *FGFR1* Rearrangement

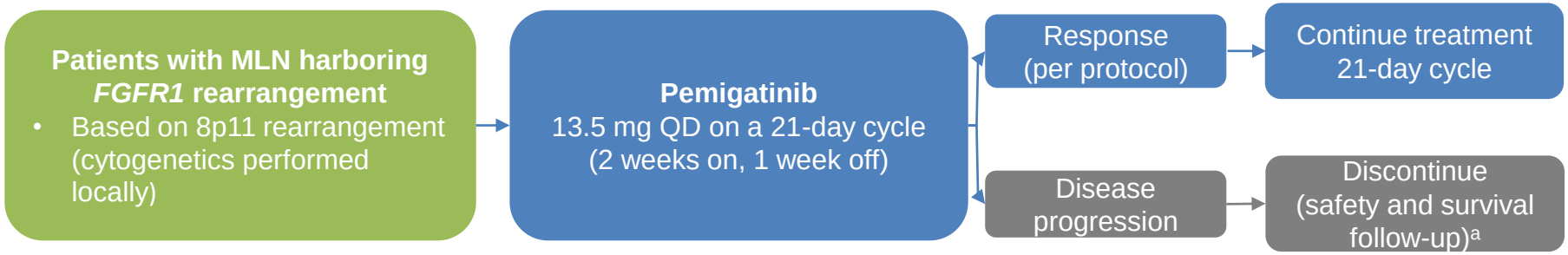
- Pemigatinib is a selective, potent, oral inhibitor of FGFR 1, 2, and 3[1]
  - Clinically active in patients with FGF/FGFR-activated tumors, such as cholangiocarcinoma and urothelial carcinoma[2,3]
- Inhibits *FGFR1*-mediated signaling and viability of a cell line harboring an 8p11 fusion

Cell line (histology)	FGFR alteration	Mean GI50 ± SD (nM)
KG-1A (AML)	FGFR1OP2-*FGFR1* fusion	3 ± 1



1. Liu PCCWL, et al. Proceedings of AACR 106th Annual Meeting 2015, 18–22 April 2015; Philadelphia, PA, abstract 771; 2. Hollebeque A, et al. *Ann Oncol.* 2018;29(suppl 8, 1 October 2018) https://doi.org/10.1093/annonc/mdy282.139. 3. Necchi A, et al. *Ann Oncol.* 2018;29(suppl9, 1 October 2018); https://doi.org/10.1093/annonc/mdy283.109.

fight-203: A Phase 2, Open-label, Multicenter Study



[a] Patients who discontinue and bridge to HSCT are followed

Key Eligibility Criteria

- Not a candidate for HSCT or relapsed after HSCT and delayed lymphocyte infusion, and progressed and not a candidate for other therapies
- Adequate renal and hepatic function
- No active CNS disease
- No calcium and phosphate hemostasis disorders
- No evidence of clinically significant corneal or retinal disease

Data cut: September 14, 2018

Primary modes of Assessment

BM Histopathology and Cytogenetic Analysis	PET/CT Scans
• Within 6 weeks before enrollment • Day 1 of every 3 cycles • End of treatment • Every 9 weeks during follow-up[a]	• At screening • If abnormal, then on Day 15, cycle 1 and every 3 cycles • End of treatment • Every 9 weeks during follow-up

[a] Lymph node biopsy is recommended at baseline and at time of progression if patient presents with lymphadenopathy

CNS, central nervous system; CT, computed tomography; PET, positron emission tomography; QD, once daily.

Study Endpoints

Composite Primary Endpoint: Overall Clinical Benefit Rate Defined as 1 of the Following:[1,2]
Complete response (CR): normalization of BM and peripheral blood and complete resolution of EMD
Partial response (PR): normalization of peripheral blood, complete resolution of EMD, and 50% reduction of BM blasts
Complete hematologic response (CHR): normalization of peripheral blood
Clinical benefit (CB): Erythroid response, platelet response, neutrophil response, eosinophil response, and/or EMD response
Marrow response: • Complete marrow response: marrow criteria necessary for CR without normalization of peripheral blood • Partial marrow response: 50% reduction in BM blasts but remaining >5%, or reduction in grading of reticulin fibrosis from baseline on ≥2 BM evaluations spaced ≥ 2 months apart if no excess of blasts at baseline
Cytogenetic response: • Complete (CCyR): 0% 8p11 translocated metaphases or FISH • Partial (PCyR): ≥ 50% decrease from baseline in 8p11 translocated metaphases or FISH
Secondary Endpoints
Duration of response, overall survival, progression-free survival, safety and tolerability

EMD, extramedullary disease; FISH, fluorescent in situ hybridization.

1. Savona M, et al. *Blood*. 2015;125:1857-1865. 2. Baccarani M, et al. *Blood*. 2006;108;1809-1820.

Patient Disposition and Exposure

- 14 patients enrolled and were treated
  - 1 patient did not have FGFR1 8p11 rearrangement known to lead to FGFR1 activation and was excluded from the efficacy analysis

Patient Disposition

Patients enrolled	14
Patients treated	14
Treatment ongoing	6
Treatment discontinued	8
Reason for discontinuation	
Bridge to HSCT	3
Adverse event	2
Progressive disease	3

- Patients received a median of 6 cycles of pemigatinib (range, 2–25 cycles)

Demographics and Disease Characteristics

Baseline Demographics and Disease Characteristics (N=14)

Age, median (range), years	61.5 (39–78)
Sex, n (%)	
Male	7 (50)
Female	7 (50)
MLN characteristics, n (%) [a]	
MLN	3 (21)
MLN + lymphoma	2 (14)
MLN + myeloid sarcoma	3 (21)
MLN blast phase	5 (36)
Prior therapies, median (range), n[b]	2 (0–4)
ECOG PS	
0	5 (36)
1	8 (57)
2	1 (7)

ECOG PS, Eastern Cooperative Oncology Group performance status.

[a] One patient in the MLN group did not have *FGFR1* 8p11 rearrangement known to lead to *FGFR1* activity and was excluded from the efficacy analysis but was included in safety analysis

[b] One patient was identified as not having received prior therapy

Clinical and Cytogenetic Responses

Age/Sex	Disease	Fusion Partner[a]	Prior Therapy	Clinical Response[b]	Response in EMD	Cytogenetic Response[c]
48 F	MLN	BCR	HU	**CR**	-	**CCyR**
39 F	MLN (aCML)	BCR	HU, ponatinib	**CR**	-	**PCyR**
66 F	MLN + splenomegaly	TPR and ZMYM2	HU	**CR**	-	**PCyR**
71 M	MLN + EMD (lymphoma[d])	ZMYM2	Hyper CVAD, steroids	**CR**	-	**CCyR**
50 M	MLN + EMD (lymphoma)	ZMYM2	CHOEP	**CR**	**CR**	**CCyR**
78 F	MLN + EMD (myeloid sarcoma)	ZMYM2	MITO-FLAG, dauno	**PR**	**SD**	**PCyR**
63 M	MLN + EMD (myeloid sarcoma)	ZMYM2	None	**PR**	**PD**	**CCyR**
60 M	MLN + EMD (myeloid sarcoma)	ZMYM2	FLAI	**PR**	**PD**	**CCyR**

CBC, complete blood count; NGS, next-generation sequencing; PD, progressive disease; SD, stable disease

[a] Fusion partners listed were determined by NGS retrospectively and were not used to assess patient eligibility

[b] CR: bone marrow (BM) with <5% blasts and normal cellularity, normal CBC, complete resolution of EMD; PR, same as CR except 50% reduction of BM blasts (and blast equivalents), but with <5% remaining fibrosis and dysplasia.

[c] CCyR: 0% abnormal metaphases; PCyR: decrease of ≥50% of abnormal metaphases

[d] Not present at baseline

Clinical and Cytogenetic Responses

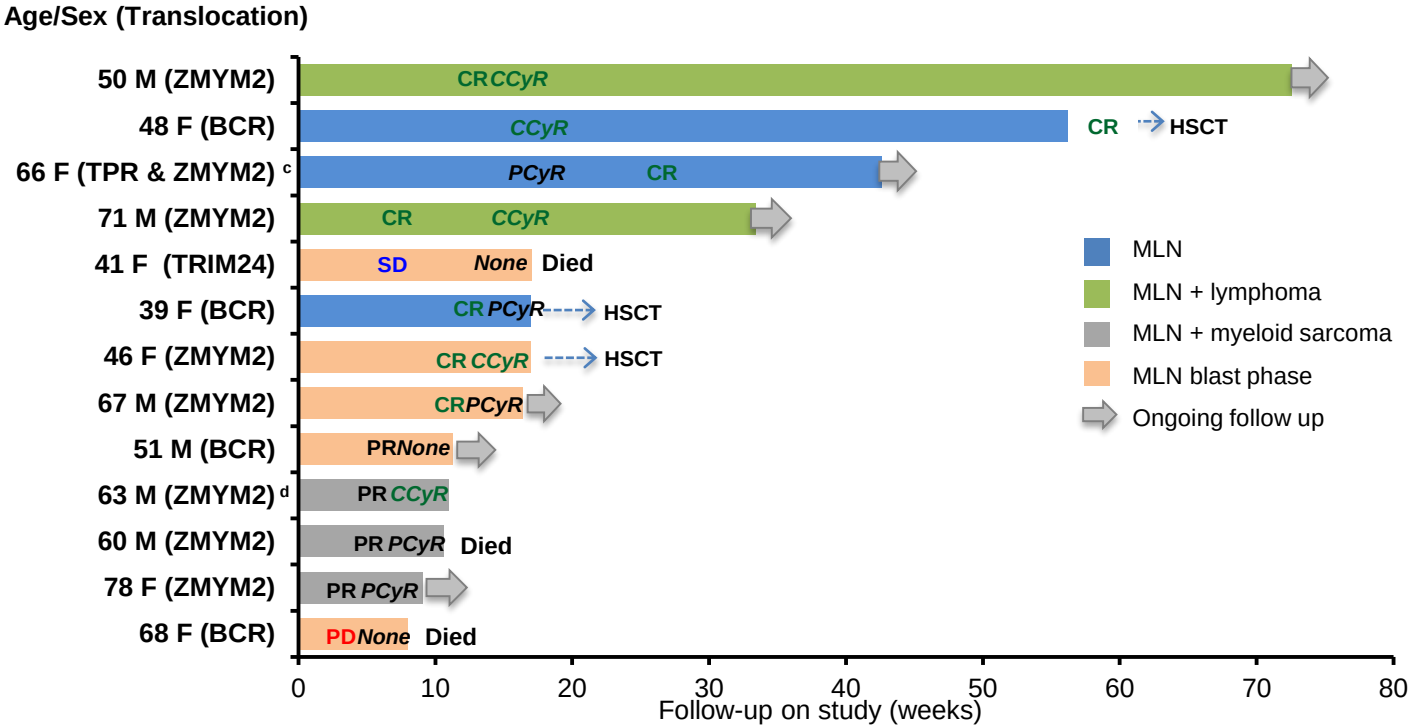
Age/Sex	Disease	Fusion Partner[a]	Prior Therapy	Clinical Response[b]	Response in EMD	Cytogenetic Response[c]
68 F	MLN blast phase (lymphoid)	BCR	NILG-ALL, Blina, HU, MTX-Ara-C	**PD** (myeloid blast crisis)	-	None
67 M	MLN blast phase (lymphoid)	BCR	HU, HSCT	**CR**	-	**PCyR**
46 F	MLN blast phase (lymphoid)	ZMYM2	R-IEV, FLA, ponatinib	**CR**	-	**CCyR**
51 M	MLN blast phase (myeloid)	BCR	CLAG-M	**PR**	-	None
41 F	MLN blast phase (myeloid)	TRIM24	3+7, MEC, FLAI, AraC	**SD**	-	None

[a] Fusion partners listed were determined by NGS retrospectively, and were not used to assess patient eligibility

[b] CR: bone marrow (BM) with <5% blasts and normal cellularity, normal CBC, complete resolution of EMD; PR, same as CR except 50% reduction of BM blasts (and blast equivalents), but with <5% remaining fibrosis and dysplasia.

[c] CCyR: 0% abnormal metaphases; PCyR: decrease of ≥50% of abnormal metaphases

Clinical and Cytogenetic Responses: Summary



[a] CR, bone marrow with < 5% blasts and normal cellularity, normal CBC, complete resolution of EMD; PR, same as CR except 50% reduction of bone marrow blasts (and blast equivalents), but with < 5% remaining fibrosis and dysplasia. [b] CCyR, 0% abnormal metaphases; PCyR, decrease of ≥50% of abnormal metaphases. [c] Switched to continuous dosing on Cycle 15. [d] Patient did not receive prior therapy

Clinical and Cytogenetic Responses: Summary (cont)

- 11 of 13 (85%) evaluable patients achieved clinical response, including clinical and cytogenetic responses

Best Responses	ORR	CR (n)	PR (n)
Clinical responses[a]	85%	7	4
Cytogenetic responses[b]	77%	6	4

[a] CR, bone marrow with < 5% blasts and normal cellularity, normal CBC, complete resolution of EMD; PR, same as CR except 50% reduction of bone marrow blasts (and blast equivalents), but with < 5% remaining fibrosis and dysplasia.

[b] CCyR, 0% abnormal metaphases; PCyR, decrease of ≥50% of abnormal metaphases.

Patient Vignette: *ZMYM2–FGFR1* Fusion

Baseline Characteristics

- 50-year-old male
- Presented with myeloproliferation and TLL
- Received CHOEP chemotherapy with no response
- Para-aortic lymphadenopathy and large spleen
- Cytogenetics: 46,XY,t(1;8;13)(p36.2;p11.2;q12) in all 10 metaphases = *ZMYM2–FGFR1*

Pemigatinib Treatment

- 13.5 mg QD; 2 weeks on 1 week off
- Achieved complete cytogenetic remission and complete lymph node remission on PET scan at 4 months (beginning of Cycle 6)
- Splenomegaly resolved
- Currently remains on treatment >1.5 years with minimal side effects

LN, lymph node.

Treatment-emergent Adverse Events (TEAEs)

- Pemigatinib was generally well tolerated
- The most common treatment-related AEs (TRAEs) were hyperphosphatemia (n=9; 64%; managed with diet and phosphate binders), diarrhea (n=5; 36%), alopecia (n=4; 29%), increased blood alkaline phosphatase (n=3; 21%), dyspepsia, and fatigue, and stomatitis (n=2; 14% each)
  - Three patients had grade 3 TRAEs: diarrhea (n=1; led to dose reduction); leukopenia (n=1); and alkaline phosphatase increase (n=1; led to discontinuation of pemigatinib)
- Two patients had fatal TEAEs unrelated to treatment
  - One patient due to multiorgan failure and disease progression
  - One patient due to chloroma, myeloid sarcoma, and septic shock

Conclusions

- Pemigatinib showed clinical and cytogenetic activity
  - Clinical response rate was 85%: CR in 7 patients and PR in 4 patients
  - Major cytogenetic response rate was 77%: CCyR in 6 patients, and PCyR in 4 patients
- Pemigatinib was generally well tolerated by patients in this study
- The fight-203 protocol was amended to allow continuous pemigatinib dosing and is currently recruiting