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POSTER ABSTRACTS

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Deep and Durable Cytogenetic and Molecular Responses with Pemigatinib in Myeloid/Lymphoid Neoplasms with Fibroblast Growth Factor Receptor 1 Rearrangement: The Fight-203 Study

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Introduction:Myeloid/lymphoid neoplasmswith fibroblast growth factor receptor 1 rearrangement (MLN ^{FGFR1}) are aggressive hematologic neoplasms caused by various reciprocal translocations involving chromosome band 8p11, resulting in tyrosine kinase fusion genes (eg, *ZMYM2::FGFR1* from t[8;13][p11;q12] or *BCR::FGFR1* from t[8;22][p11;q11]) and constitutive *FGFR1* activationand downstream signaling. Pemigatinib is a potent and selective oral inhibitor of FGFR1-3 approved for the treatment of adults with relapsed or refractory MLN ^{FGFR1}. Efficacy and safety data for 41 patients with MLN ^{FGFR1} in the ongoing FIGHT-203 study of pemigatinib were previously reported. Median daily pemigatinib dose was 9.5 mg; treatment-emergent adverse events led to dose interruptions in 66% of patients. Rates of complete response (CR) among the 38 patients evaluable for clinical response and rates of complete cytogenetic response (CCyR) for the 40 patients evaluable for cytogenetic response were 74% and 70%, respectively. CR and CCyR occurred in >80% of patients with chronic phase disease and in >50% of patients with blast phase disease. Here we present an analysis of centralized fluorescence in situ hybridization (FISH) evaluation of bone marrow (BM) cells and serial characterization of levels of *FGFR1* fusion transcripts in this same cohort.
Methods: FIGHT-203 (NCT03011372) is an ongoing open-label, multicenter, phase 2 study evaluating pemigatinib in patients ≥18 years old with MLN ^{FGFR1} and ≥1 prior therapy. The starting dose was pemigatinib 13.5 mg daily (2 weeks on, 1 week off). Following protocol amendments, patients without prior therapy were eligible to enroll, and the dosing regimen was changed to a continuous schedule. Patients were censored for cytogenetic and molecular follow-up at the time of transplantation. CCyR was defined as 0 metaphases positive for the respective reciprocal translocation in ≥20 evaluated BM metaphases on local and/or central karyotyping or 0 cells (or not exceeding the lower level of detection of the probe) with the *FGFR1* rearrangement in ≥200 BM cells on local and/or central break-apart FISH assays (central FISH prioritized). As part of the translational research plan, fusion partner genes were identified with next-generation sequencing (NGS; FusionPlex, Archer, Boulder, CO, USA) and

targeted PCR profiling of RNA extracted from whole blood; droplet digital PCR (ddPCR) assays were developed to monitor the frequencies of specific *FGFR1* fusion transcripts in RNA extracted from whole blood samples (estimated limit of detection, 0.05 copies/μL).

Results: As of June 30, 2021, 39 of 41 enrolled and treated patients were evaluable for translational analyses. Among the 39 patients with whole blood samples, *FGFR1* fusion partner genes identified on translational testing were *ZMYM2* (n=17), *BCR* (n=11), *FGFR1OP* (n=4), *TPR* (n=3), *TRIM24* (n=2), and *C14orf93*, *CCDC6, CNTRL* and *ETV6* (n=1 each). Two of 39 patients had 2 fusions detected (*ZMYM2* and *BCR*, n=1; *ZMYM2* and *TPR*, n=1). *C14orf93*, *CCDC6* and *ETV6* have not been previously identified as *FGFR1* fusion partner genes. Central FISH assessment of BM cells confirmed *FGFR1*-aberrantcells were reduced to undetectable levels in responding patients but rebounded in some patients during periods of treatment interruption (Figure A). Serial ddPCR of whole blood samples demonstrated marked reductions in *FGFR1* fusion transcripts for the 34 patients with ≥3 measures while on treatment (Figure B). Among patients with CR, 81.0% had a >2-log reduction and 47.6% had a >3-log reduction in detectable *FGFR1* fusion transcripts. Smaller reductions in *FGFR1* fusion transcripts were observed in patients with stable disease. Changes in *FGFR1* fusion transcripts correlated with *FGFR1* FISH results (Pearson coefficient = 0.81) and reflected changes in treatment intensity.

Conclusion:Several new *FGFR1* fusion partner genes, including *C14orf93*, *CCDC6*, and *ETV6* were identified with NGS and PCR profiling. Pemigatinib treatment resulted in marked decreases in the percentages of cells with the *FGFR1* rearrangement on FISH, as well as 2-3 log reductions in *FGFR1* fusion transcripts in patients with MLN ^{FGFR1}. Further investigations are ongoing to determine the relationship between pemigatinib dose intensity and the depth and durability of molecular response.

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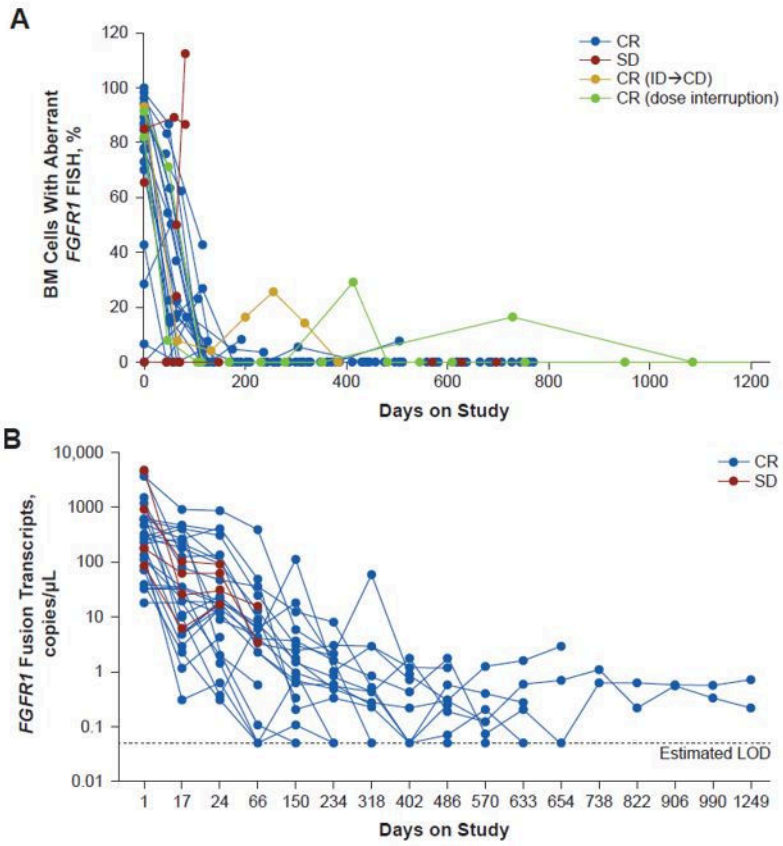
Figure. (A) Summary of Central *FGFR1*-FISH Analysis of BM Cells (N=39) and (B) *FGFR1* Fusion Transcript Levels in Patients With ≥3 Measures of Fusion Frequency (N=34)



BM, bone marrow; CD, continuous dosing; CR, complete response; FGFR, fibroblast growth factor receptor; FISH, fluorescence in situ hybridization; ID, intermittent dosing; LOD, limit of detection; SD, stable disease.

Figure 1

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