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POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Ibrutinib, Fludarabine, Cyclophosphamide and Obinutuzumab (iFCG) for Firstline Treatment of Patients with CLL with Mutated *IGHV* and without Del(17p)/ *TP53* Mutation: Six-Year Follow-up Analyses

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Background

Patients (pts) with *IGHV*-mutated (*IGHV*-M) CLL have favorable long-term outcomes after receiving first-line FCR (fludarabine, cyclophosphamide and rituximab). We designed an investigator-initiated, phase II trial with ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab (iFCG) for previously untreated pts with *IGHV*-M CLL (NCT02629809), and we report here an updated analysis with a median follow-up of 72 months.

Methods

Inclusion criteria included diagnosis of previously untreated CLL/SLL needing treatment per iwCLL criteria, age ≥18, *IGHV*-M, absence of both del(17p) and *TP53* mutation. Pts received 3 courses of iFCG. Pts achieving CR/CRi with undetectable MRD (U-MRD) in bone marrow (BM) (4-color flow-cytometry, sensitivity 10^{-4}) after 3 courses of iFCG received ibrutinib with obinutuzumab (iG) for 3 cycles, followed by ibrutinib monotherapy for 6 months. All other pts received iG for 9 cycles (C4-12). Pts with U-MRD (CR/CRi or PR) at end of Cycle 12 stopped all therapy, including ibrutinib. Response assessment was per 2008 iwCLL criteria with BM and CT scans every 3 months during the first year. After completion of all therapy, pts were followed by clinical examination, blood counts and peripheral blood MRD every 6 months.

Results

Between March 2016 and August 2018, 45 pts initiated treatment. Data cutoff was July 15, 2023. Baseline characteristics are shown in Table 1. All pts per study inclusion criterion had *IGHV*-M; however, 1 enrolled pt was later reclassified as *IGHV*-unmutated. A total of 69% pts had del(13q). After three cycles of iFCG, 39/45 (87%) pts achieved marrow U-MRD. Responses improved with continued therapy with 40/45 (89%) and 41/45 (91%) achieving marrow U-MRD after Cycles 6 and 12, respectively. Overall, 44/45 (98%) pts achieved marrow U-MRD as best response at any time during the study. Median follow-up duration is 72 months.

41/45 pts completed 12 cycles of treatment (4 pts came off study prior to Cycle 12). All 41 pts achieved marrow U-MRD and per protocol, discontinued ibrutinib. After a median follow-up of 61 mos post-discontinuing ibrutinib, 8 pts had MRD recurrence (defined as 2 consecutive values of ≥0.01% in peripheral blood by flow cytometry) at a median of 32 mos (range, 20-67 mos) after stopping all therapy. Of the 8 pts with MRD recurrence, 2 pts had clinical relapse (described below); remaining 6 pts are being monitored with no clinical progression or active therapy.

The 6-year PFS and OS are 92.2% (95% CI= 77.7-97.4) and 97.7% (95% CI= 84.9-99.6), respectively. Two pts had clinical progression: one pt had *IGHV* 3-21; MRD recurred 28 mos after discontinuing ibrutinib, with clinical relapse 59 mos after discontinuing

ibrutinib; this pt is now in remission with venetoclax-based therapy; the second pt with clinical relapse had *IGHV*-unmutated CLL, MRD recurred 24 mos after discontinuing ibrutinib, with clinical relapse 48 mos after discontinuing ibrutinib; this pt has not yet required therapy for relapse. No pt had progression to Richter transformation. One pt developed therapy-related myelodysplastic syndrome; this pt is being monitored for 58+ months without any active therapy for MDS with normal blood counts. One pt died from congestive heart failure during month 9 of the study.

Conclusions

iFCG regimen with only three cycles of combination chemotherapy achieves U-MRD rates of 98% in bone marrow on an intent-to-treat analysis and a 6-year PFS of 92% in *IGHV*-M CLL. These results are favorable compared to the 5-year PFS of approximately 65% with FCR (CLL10 trial) for the same genomic subgroup. Additionally, these results also appear favorable to the current targeted therapy regimens (such as BTKi, BCL2i+CD20 antibody) for *IGHV*-M CLL. With the caveat that the role of chemoimmunotherapy in CLL has significantly declined, the iFCG regimen provides for a very high rate of durable remissions among a chemo-sensitive subgroup of pts with CLL.

Disclosures Jain: *AbbVie:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses, Research Funding; *Cellectis:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses, Research Funding; *Takeda:* Research Funding; *TG Therapeutics:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses; *Genentech:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses, Research Funding; *ADC Therapeutics:* Research Funding; *Servier:* Research Funding; *TransThera Sciences:* Research Funding; *Mingsight:* Research Funding; *Aprea Therapeutics:* Research Funding; *Beigene:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses; *Medisix:* Research Funding; *Incyte:* Research Funding; *Newave:* Research Funding; *CareDX:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses; *Ipsen:* Consultancy, Honoraria, Other: TRAVEL, ACCOMMODATIONS, EXPENSES; *MEI Pharma:* Consultancy, Honoraria, Other: TRAVEL, ACCOMMODATIONS, EXPENSES; *Fate Therapeutics:* Research Funding; 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OffLabel Disclosure: Combination of ibrutinib with FCG regimen is not FDA approved

Table 1. Characteristics of All 45 Patients at Study Entry

		Number (%) or median [range]
Age, years		60 [25-71]
Gender, Male		35 (78)
Baseline Labs	ALC, x 10^9/L Hemoglobin, g/dL Platelet count, x 10^9/L Serum B2M, mg/L	52.9 [1.5-208] 11.9 [8.5-15.6] 120 [62-292] 2.7 [1.3-8.1]
Baseline Hierarchical FISH	Del(11q) Trisomy 12 Normal Del(13q)	1 (2) 7 (16) 6 (13) 31 (69)
Baseline Cytogenetics (n=39)	Diploid	27 (69)
Baseline Gene Mutation (n=39)	*MYD88* *SF3B1* *NOTCH1* *BIRC3*	5 (13) 3 (8) 1 (3) 1 (3)

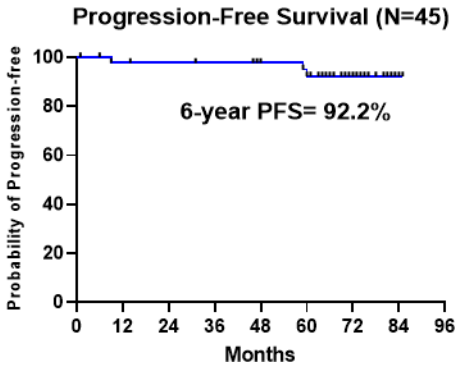

Figure 1

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