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CLL/SLL

The phase III COMPLEMENT 2 trial: ofatumumab plus FC improves PFS with manageable safety versus FC alone in patients with relapsed Chronic Lymphocytic Leukemia

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This month, in Leukemia & Lymphoma, Tadeusz Robak from the Medical University of Lodz and Copernicus Memorial Hospital, Lodz, Poland, and colleagues published results of the randomized, open-label, phase III COMPLEMENT 2 trial (NCT00824265).

The trial assessed fludarabine-cyclophosphamide plus ofatumumab (OFA+FC) versus fludarabine-cyclophosphamide (FC) alone in patients with relapsed (but not refractory) CLL. Patients were randomized 1:1 to each arm and the primary endpoint was Independent Review Committee (IRC)-assessed PFS.

In total, 365 pts enrolled; 183 patients were randomized to the OFA+FC arm and 182 to the FC arm. Median age of patients was 61 years (range, 32–90); 134 patients (37%) were over >65 years and 27 patients (7%) were over 75 years.

Key Highlights:

Treatment

- OFA+FC treatment = six 28-day cycles; ofatumumab IV (cycle 1: 300mg day 1 and 1,000mg day 8; cycles 2–6: 1,000 mg day 1) plus fludarabine IV (25mg/m^2) and cyclophosphamide IV (250mg/m^2) on days 1–3 of each cycle
- FC treatment = Fludarabine IV (25 mg/m^2) and cyclophosphamide IV (250mg/m^2) on days 1–3 for six 28-day cycles

Efficacy

- Median follow-up = 1,034 days (approx. 34 months)
- At data cut-off, pts who had progressed or died: OFA+FC = 56%; FC = 58%
- IRC median PFS: OFA+FC = 28.9 months; FC = 18.8 months (HR, 0.67; 95% CI, 0.51–0.88; *P* = 0.0032)
- Investigator median PFS: OFA+FC = 27.2 months; FC = 16.8 months (HR, 0.66; 95% CI, 0.51–0.85; *P* = 0.0009)
- IRC median EFS: OFA+FC = 27.2 months; FC = 16.5 months (HR, 0.66; 95% CI, 0.51–0.86; *P* = 0.0012)
- IRC time to progression: OFA+FC = 42.1 months; FC = 26.8 months (HR, 0.63; 95% CI, 0.45–0.87; *P* = 0.0036)
- Median OS: OFA+FC = 56.4 months; FC = 45.8 months (HR, 0.78; 95% CI, 0.56–1.09; *P* = 0.1410)
- IRC ORR: OFA+FC = 153 (84%); FC = 123 (68%; *P* = 0.0003)
- CR: OFA+FC = 49 (27%); FC = 13 (7%)
- MRD negativity at 3 months after last treatment: OFA+FC = 39 (21%); FC = 15 (8%; *P* = 0.0006)
- MRD negativity at 6 months after last treatment: OFA+FC = 48 (26%); FC = 11 (6%; *P* < 0.0001)

- Time to next anticancer therapy: OFA+FC = 48.1 months; FC = 40.1 months (HR, 0.73; 95% CI, 0.51–1.05; *P* = 0.0735)
- IRC time to response: OFA+FC = 1.0 month; FC = 1.0 month (HR, 1.08; 95% CI, 0.85–1.37; *P* = 0.4490)
- IRC DoR: OFA+FC = 29.6 months; FC = 24.9 months (HR, = 0.77; 95% CI, 0.56–1.05; *P* = 0.0878)

Safety

- AEs of any grade: OFA+FC = 169 (93%); FC = 151 (85%)
- AEs of grade 3: OFA+FC = 134 (74%); FC = 123 (69%)
- AEs leading to treatment discontinuation: OFA+FC = 49 (27%); FC = 49 (28%)
- Neutropenia was the most common AE, any grade: OFA-FC = 108 60%; FC = 77 (43%)
- Thrombocytopenia and anemia were more common in FC pts than OFA+FC pts
- Infections: OFA+FC = 70 (39%); FC = 65 (37%)
- Fatal infections: OFA+FC = 5 (3%); FC = 3 (2%)
- Infusion related reactions: OFA+FC = 108 (60%), caused withdrawal in 5 pts; FC = 50 (28%)
- The most frequent treatment-related AEs (in >10% of pts) in OFA+FC and FC pts were neutropenia (58% vs. 41%), thrombocytopenia (26% vs. 32%), nausea (19% in both arms), anemia (15% vs. 26%), and leukopenia (14% vs. 6%)
- A total of 38 pts (OFA+FC = 18; FC = 20) reported grade 3–4 neutropenia that occurred during treatment and had not resolved within 42 days of the last treatment dose
- Late-onset neutropenia (grade 3–4 starting ≥42 days after last treatment dose) was reported in 18 pts (OFA+FC = 13 [7%]; FC = 5 [3%])
- Deaths during treatment or ≤30 days post-treatment: 3 (2%) OFA+FC pts and 4 (2%) FC pts
- A further 8 deaths occurred from 30–60 days after last dosing, 2 (1%) in OFA+FC pts and 6 (3%) in FC pts
- CLL caused 32 /67 (18%) deaths in the OFA+FC arm and 31/69 (17%) deaths in the FC arm

The authors concluded that combining ofatumumab with fludarabine and cyclophosphamide demonstrated a “manageable safety profile” and showed “clinically important improvements in efficacy compared to FC alone” in patients with relapsed CLL.

Abstract:

In this multicenter, open-label, phase III study, patients with relapsed chronic lymphocytic leukemia (CLL) were randomized (1:1) to receive ofatumumab plus fludarabine and cyclophosphamide (OFA + FC) or FC alone; the primary endpoint being progression-free survival (PFS) assessed by an independent review committee (IRC). Between March 2009 and January 2012, 365 patients were randomized (OFA + FC: n = 183; FC: n = 182). Median IRC-assessed PFS was 28.9 months with OFA + FC versus 18.8 months with FC (hazard ratio = 0.67; 95% confidence interval, 0.51-0.88; p = .0032). Grade ≥3 adverse events (≤60 days after last dose) were reported in 134 (74%) OFA + FC-treated patients compared with 123 (69%) FC-treated patients. Of these, neutropenia was the most common (89 [49%] vs. 64 [36%]). OFA + FC improved PFS with manageable safety for patients with relapsed CLL compared with FC alone, thus providing an alternative treatment option for patients with relapsed CLL.

Reference:

1. Robak T. *et al.* Ofatumumab plus fludarabine and cyclophosphamide in relapsed chronic lymphocytic leukemia: results from the COMPLEMENT 2 trial. Leukemia & Lymphoma. 2017 May;58(5):1084-1093. DOI: 10.1080/10428194.2016.1233536. Epub 2016 Oct 12.